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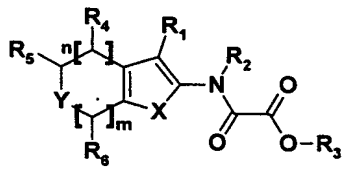
Modulators of Protein Tyrosine Phosphatases (PTPases)

FIELD OF THE INVENTION

The present invention relates to novel compounds, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, where such compounds of Formula 1 are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPases) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like,



Formula 1

wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined more fully below.

It has been found that PTPases plays a major role in the intracellular modulation and regulation of fundamental cellular signaling mechanisms involved in metabolism, growth, proliferation and differentiation (Hunter, Phil. *Trans. R. Soc. Lond.* B 353: 583-605 (1998); Chan *et al., Annu. Rev. Immunol.* 12: 555-592 (1994); Zhang, *Curr. Top. Cell. Reg.* 35: 21-68 (1997); Matozaki and Kasuga, *Cell. Signal.* 8: 113-19 (1996); Flint *et al., The EMBO J.* 12:1937-46 (1993); Fischer *et al, Science* 253:401-6 (1991)). Overexpression or altered activity of tyrosine phosphatases can also contribute to the symptoms and progression of various diseases (Wiener, *et al., J. Natl. cancer Inst.* 86:372-8 (1994); Hunter and Cooper, *Ann. Rev. Biochem*, 54:897-930 (1985)). Furthermore, there is increasing evidence which suggests that inhibition of these PTPases may help treat certain types of diseases such as diabetes type I and II, autoimmune disease, acute and chronic inflammation, osteoporosis and various forms of cancer.

BACKGROUND OF THE INVENTION

Protein phosphorylation is now well recognized as an important mechanism utilized by cells to transduce and regulate signals during different stages of cellular function (Hunter, *Phil. Trans. R. Soc. Lond.* B *353*: 583-605 (1998); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Zhang, *Curr. Top. Cell. Reg. 35*: 21-68 (1997); Matozaki and Kasuga, *Cell. Signal. 8*: 113-19 (1996); Fischer *et al, Science 253*:401-6 (1991); Flint *et al., EMBO J. 12*:1937-46 (1993)). There are at least two major classes of phosphatases: (1) those that dephosphorylate proteins (or peptides) that contain a phosphate group(s) on a serine or threonine moiety (termed Ser/Thr phosphatases) and (2) those that remove a phosphate group(s) from the amino acid tyrosine (termed protein tyrosine phosphatases or PTPases or PTPs).

The PTPases are a family of enzymes that can be classified into two groups: a) intracellular or nontransmembrane PTPases and b) receptor-type or transmembrane PTPases.

Intracellular PTPases: Most known intracellular type PTPases contain a single conserved catalytic phosphatase domain consisting of 220-240 amino acid residues. The regions outside the PTPase domains are believed to play important roles in localizing the intracellular PTPases subcellularly (Mauro, L.J. and Dixon, J.E. *TIBS 19*: 151-155 (1994)). The first intracellular PTPase to be purified and characterized was **PTP1B**, which was isolated from human placenta (Tonks *et al., J. Biol. Chem. 263*: 6722-6730 (1988)). Shortly after, PTP1B was cloned (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989); Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)). Other examples of intracellular PTPases include (1) **T-cell PTPase/ TC-PTP** (Cool *et al. Proc. Natl. Acad. Sci. USA 86*: 5257-5261 (1989)),

(2) **rat brain PTPase** (Guan *et al., Proc. Natl. Acad. Sci. USA 87*:1501-1502 (1990)), (3) neuronal phosphatase **STEP** (Lombroso *et al., Proc. Natl. Acad. Sci. USA 88*: 7242-7246 (1991)), (4) ezrin-domain containing PTPases: **PTPMEG1** (Gue*t al., Proc. Natl. Acad. Sci. USA 88*: 5867-57871 (1991)), **PTPH1** (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)), **PTPD1 and PTPD2** (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)), **FAP-1/BAS** (Sato *et al., Science 268*: 411-415 (1995); Banville *et al., J. Biol. Chem. 269*: 22320-22327 (1994); Maekawa *et al., FEBS Letters 337*: 200-206 (1994)), and SH2 domain containing PTPases: **PTP1C/SH-PTP1/SHP-1** (Plutzky *et al., Proc. Natl. Acad. Sci. USA 89*: 1123-1127 (1992); Shen *et al., Nature Lond. 352*: 736-739 (1991)) and **PTP1D/Syp/SH-PTP2/SHP-2** (Vogel *et al., Science 259*: 1611-1614 (1993); Feng *et al., Science 259*: 1607-1611 (1993); Bastein *et al., Biochem. Biophys. Res. Comm. 196*: 124-133 (1993)).

Receptor-type PTPases consist of a) a putative ligand-binding extracellular domain, b) a transmembrane segment, and c) an intracellular catalytic region. The structures and sizes of the putative ligand-binding extracellular domains of receptor-type PTPases are quite divergent. In contrast, the intracellular catalytic regions of receptor-type PTPases are very homologous to each other and to the intracellular PTPases. Most receptor-type PTPases have two tandemly duplicated catalytic PTPase domains.

The first receptor-type PTPases to be identified were (1) **CD45/LCA** (Ralph, S.J., *EMBO J. 6*: 1251-1257 (1987)) and (2) **LAR** (Streuli *et al., J. Exp. Med. 168*: 1523-1530 (1988)) that were recognized to belong to this class of enzymes based on homology to PTP1B (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989)). CD45 is a family of high molecular weight glycoproteins and is one of the most abundant leukocyte cell surface glycoproteins and appears to be exclusively

expressed upon cells of the hematopoietic system (Trowbridge and Thomas, *Ann. Rev. Immunol. 12*: 85-116 (1994)).

The identification of CD45 and LAR as members of the PTPase family was quickly followed by identification and cloning of several different members of the receptor-type PTPase group. Thus, 5 different PTPases, (3) **PTPα**, (4) **PTPβ**, (5) **PTPδ**, (6) **PTPε**, and (7) **PTPζ**, were identified in one early study (Krueger *et al., EMBO J. 9*: 3241-3252 (1990)). Other examples of receptor-type PTPases include (8) **PTPγ** (Barnea *et al., Mol. Cell. Biol. 13*: 1497-1506 (1995)) which, like **PTPζ** (Krueger and Saito, *Proc. Natl. Acad. Sci. USA 89*: 7417-7421 (1992)) contains a carbonic anhydrase-like domain in the extracellular region, (9) **PTPμ** (Gebbink *et al., FEBS Letters 290*: 123-130 (1991)), (10) **PTPκ** (Jiang *et al., Mol. Cell. Biol. 13*: 2942-2951 (1993)). Based on structural differences the receptor-type PTPases may be classified into subtypes (Fischer *et al., Science 253*: 401-406 (1991)): (I) CD45; (II) LAR, PTPd, (11) **PTPσ** ; (III) **PTPb**, (12) **SAP-1** (Matozaki *et al., J. Biol. Chem. 269*: 2075-2081 (1994)), (13) **PTP-U2/GLEPP1** (Seimiya *et al., Oncogene 10*: 1731-1738 (1995); Thomas *et al., J. Biol. Chem. 269*: 19953-19962 (1994)), and (14) **DEP-1**; (IV) **PTPa,_PTPe**. All receptor-type PTPases except Type III contain two PTPase domains. Novel PTPases are continuously identified, and it is anticipated that more than 500 different species will be found in the human genome, i.e. close to the predicted size of the protein tyrosine kinase superfamily (Hanks and Hunter, *FASEB J. 9*: 576-596 (1995)).

PTPases are the biological counterparts to protein tyrosine kinases (PTKs). Therefore, one important function of PTPases is to control, down-regulate, the activity of PTKs. However, a more complex picture of the function of PTPases has emerged. Thus, several studies have shown that some PTPases may actually act as positive mediators of cellular signaling. As an example, the SH2 domain-containing SHP-2

seems to act as a positive mediator in insulin-stimulated Ras activation (Noguchi *et al., Mol. Cell. Biol. 14*: 6674-6682 (1994)) and of growth factor-induced mitogenic signal transduction (Xiao *et al., J. Biol. Chem. 269*: 21244-21248 (1994)), whereas the homologous SHP-1 seems to act as a negative regulator of growth factor-stimulated proliferation (Bignon and Siminovitch, *Clin.Immunol. Immunopathol. 73*: 168-179 (1994)). Another example of PTPases as positive regulators has been provided by studies designed to define the activation of the Src-family of tyrosine kinases. In particular, several lines of evidence indicate that CD45 is positively regulating the activation of hematopoietic cells, possibly through dephosphorylation of the C-terminal tyrosine of Fyn and Lck (Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994)).

PTPases were originally identified and purified from cell and tissue lysates using a variety of artificial substrates and, therefore, their natural function of dephosphorylation was not well known. Since tyrosine phosphorylation by tyrosine kinases is usually associated with cell proliferation, cell transformation and cell differentiation, it was assumed that PTPases were also associated with these events. This association has now been proven to be the case with many PTPases. PTP1B, a phosphatase whose structure was the first PTPase to be elucidated (Barford *et al., Science* 263:1397-1404 (1994)) has been shown to be involved in insulin-induced oocyte maturation (Flint *et al., The EMBO J.* 12:1937-46 (1993)) and recently it has been suggested that the overexpression of this enzyme may be involved in $p185^{c\text{-}erb\ B2}$-associated breast and ovarian cancers (Wiener, *et al., J. Natl. cancer Inst.* 86:372-8 (1994); Weiner *et al., Am. J. Obstet. Gynecol.* 170:1177-883 (1994)). The insulin-induced oocyte maturation mechanism has been correlated with the ability of PTP1B to block activation of S6 kinase. The association with cancer is recent evidence which suggests that overexpression of PTP1B is statistically correlated with increased levels of $p185^{c\text{-}erb\ B2}$ in ovarian and breast cancer. The role of PTP1B in the etiology and progression of the

disease has not yet been elucidated. Inhibitors of PTP1B may therefore help clarify the role of PTP1B in cancer and in some cases provide therapeutic treatment for certain forms of cancer.

PTPases: the insulin receptor signaling pathway/diabetes

Insulin is an important regulator of different metabolic processes and plays a key role in the control of blood glucose. Defects related to its synthesis or signaling lead to diabetes mellitus. Binding of insulin to the insulin receptor (IR) causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the b-subunit. Three closely positioned tyrosine residues (the tyrosine-1150 domain) must all be phosphorylated to obtain full activity of the insulin receptor tyrosine kinase (IRTK) which transmits the signal further downstream by tyrosine phosphorylation of other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden *et al., J. Biol. Chem. 267*: 16660-16668 (1992); Myers and White, *Diabetes 42*: 643-650 (1993); Lee and Pilch, *Am. J. Physiol. 266*: C319-C334 (1994); White *et al., J. Biol. Chem. 263*: 2969-2980 (1988)). The structural basis for the function of the tyrosine-triplet has been provided by recent X-ray crystallographic studies of IRTK that showed tyrosine-1150 to be autoinhibitory in its unphosphorylated state (Hubbard *et al., Nature 372*: 746-754 (1994)) and of the activated IRTK (Hubbard, *EMBO J.* 16:5572-5581 (1997)).

Several studies clearly indicate that the activity of the auto-phosphorylated IRTK can be reversed by dephosphorylation *in vitro* (reviewed in Goldstein, *Receptor 3*: 1-15 (1993); Mooney and Anderson, *J. Biol. Chem. 264*: 6850-6857 (1989)), with the tri-phosphorylated tyrosine-1150 domain being the most sensitive target for protein-tyrosine phosphatases (PTPases) as compared to the di- and mono- phosphorylated forms (King *et al., Biochem. J. 275*: 413-418 (1991)). It is, therefore, tempting to speculate that this tyrosine-triplet

functions as a control switch of IRTK activity. Indeed, the IRTK appears to be tightly regulated by PTP-mediated dephosphorylation *in vivo* (Khan *et al., J. Biol. Chem. 264*: 12931-12940 (1989); Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992); Rothenberg *et al., J. Biol. Chem. 266*: 8302-8311 (1991)). The intimate coupling of PTPases to the insulin signaling pathway is further evidenced by the finding that insulin differentially regulates PTPase activity in rat hepatoma cells (Meyerovitch *et al., Biochemistry 31*: 10338-10344 (1992)) and in livers from alloxan diabetic rats (Boylan *et al., J. Clin. Invest. 90*: 174-179 (1992)).

Until recently, relatively little was known about the identity of the PTPases involved in IRTK regulation. However, the existence of PTPases with activity towards the insulin receptor can be demonstrated as indicated above. Further, when the strong PTPase-inhibitor pervanadate is added to whole cells an almost full insulin response can be obtained in adipocytes (Fantus *et al.*, *Biochemistry 28*: 8864-8871 (1989); Eriksson *et al.*, *Diabetologia 39*: 235-242 (1995)) and skeletal muscle (Leighton *et al.*, *Biochem. J. 276*: 289-292 (1991)). In addition, recent studies show that a new class of peroxovanadium compounds act as potent hypoglycemic compounds *in vivo* (Posner *et al.*,*supra*). Two of these compounds were demonstrated to be more potent inhibitors of dephosphorylation of the insulin receptor than of the EGF-receptor.

It was recently found that mice lacking the protein tyrosine phosphatase-1B gene (PTP1B) (Elchebly *et al.*, *Science 283:* 1544-1548 (1999)) yielded healthy mice that, in the fed state, had blood glucose concentrations that were slightly lower and concentrations of circulating insulin that were one-half those of their PTP-1B$^{+/+}$ littermates. The enhanced insulin sensitivity of the PTP$^{-/-}$ mice was also evident in glucose and insulin tolerance tests. The PTP-1B$^{-/-}$ mice showed increased phosphorylation of the insulin receptor in liver and muscle tissue after insulin injection in comparison to PTP-1B$^{+/+}$ mice. This

results points in the direction that PTP1B has a major role in modulating both insulin sensitivity and fuel metabolism, thereby establishing it as a target in treatment of for example, type II diabetes and obesity.

Previous findings are in accordance with the results reported by Elchebly *et al.* (supra). Thus, it has been found that high glucose concentration induce insulin resistance and increase the expression of PTP1B in rat (fibroblasts expressing the human insulin receptor (Maegawa *et al.*, *J. Biol. Chem. 270:* 7724-7730 (1995)). Importantly, it was further found that thiazolidine derivatives ameliorate said insulin resistance via normalization of PTPase activities. In rat L6 cells, insulin and insulin-like growth factor I (IGF-I) were found to induce increased PTPase activity, including increased PTP1B expression (Kenner *et al. J. Biol. Chem. 266:* 25455-25462 (1993)). In addition, the same group has shown that PTP1B may interact directly with the activated IR (Seely *et al. Diabetes 45:* 1379-1385 (1996)) and act directly as a negative regulator of insulin and IGF-I-stimulated signaling (Kenner *et al. J. Biol. Chem. 271:* 19810-19816 (1996)). Osmotic loading of rat KRC-7 hepatoma cells with neutralizing anti-PTP1B antibodies also indicated a role for PTP1B in negative regulating of the insulin signaling pathway (Akmad *et al. J. Biol. Chem. 270:* 20503-20508 (1995)).

Also other PTPases have been implicated as regulators of the insulin signaling pathway. Thus, it was found that the ubiquitously expressed SH2 domain containing PTPase, PTP1D/SHP-2 (Vogel *et al.*, 1993, *supra*), associates with and dephosphorylates IRS-1, but apparently not the IR itself (Kuhné *et al., J. Biol. Chem. 268*: 11479-11481 (1993); (Kuhné *et al., J. Biol. Chem. 269*: 15833-15837 (1994)).

Other studies suggest that receptor-type or membrane-associated PTPases are involved in IRTK regulation (Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992), (Häring *et al., Biochemistry 23*: 3298-3306 (1984); Sale, *Adv. Prot. Phosphatases 6*: 159-186 (1991)). Hashimoto *et al.* have proposed that LAR might play a role in the physiological regulation of insulin receptors in intact cells (Hashimoto *et*

al., J. Biol. Chem. 267: 13811-13814 (1992)). Their conclusion was reached by comparing the rate of dephosphorylation/inactivation of purified IR using recombinant PTP1B as well as the cytoplasmic domains of LAR and PTPa. Antisense inhibition was used to study the effect of LAR on insulin signaling in a rat hepatoma cell line (Kulas *et al., J. Biol. Chem. 270*: 2435-2438 (1995)). A suppression of LAR protein levels by about 60 percent was paralleled by an approximately 150 percent increase in insulin-induced auto-phosphorylation. However, only a modest 35 percent increase in IRTK activity was observed, whereas the insulin-dependent phosphatidylinositol 3-kinase (PI 3-kinase) activity was significantly increased by 350 percent. Reduced LAR levels did not alter the basal level of IRTK tyrosine phosphorylation or activity. The authors speculate that LAR could specifically dephosphorylate tyrosine residues that are critical for PI 3-kinase activation either on the insulin receptor itself or on a downstream substrate.

While previous reports indicate a role of PTPa in signal transduction through src activation (Zheng *et al., Nature 359*: 336-339 (1992); den Hertog *et al., EMBO J. 12*: 3789-3798 (1993)) and interaction with GRB-2 (den Hertog *et al., EMBO J. 13*: 3020-3032 (1994); Su *et al., J. Biol. Chem. 269*: 18731-18734 (1994)), Møller, Lammers and coworkers provided results that suggest a function for this phosphatase and its close relative PTPe as negative regulators of the insulin receptor signal (Møller *et al.*, 1995 *supra*; Lammers, *et al.* , *FEBS Lett.* 404:37-40 (1997). These studies also indicated that receptor-like PTPases may play a significant role in regulating the IRTK. In this particular system intracellular PTPases seemed to have little, if any, activity towards the insulin receptor it self. While it appears that the target of the negative regulatory activity of PTPases a and e is the receptor itself, the down modulating effect of the intracellular PTP1B and TC-PTP seems to be due to a downstream function in the IR-activated signal. Both PTPases have distinct structural features that determine their

subcellular localization and thereby their access to defined cellular substrates (Frangione *et al., Cell 68*: 545-560 (1992); Faure and Posner, *Glia 9*: 311-314 (1993)). Therefore, the lack of activity of PTP1B and TC-PTP towards the IRTK may, at least in part, be explained by the fact that they do not colocalize with the activated insulin receptor. In support of this view, PTP1B and TC-PTP have been excluded as candidates for the IR-associated PTPases in hepatocytes based on subcellular localization studies (Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992)). However, it should be noted that a direct effect on the insulin receptor was observed in the above described PTP1B knock-out mice (Elcheby *et al.*, supra). The reason for these discrepancies is not known at present.

Other studies have shown that PTP1B and TC-PTP are likely to be involved in the regulation of several other cellular processes in addition to the described regulatory roles in insulin signaling. Therefore, PTP1B and/or TC-PTP as well as other PTPases showing key structural features with PTP1B and TC-PTP are likely to be important therapeutic targets in a variety of human and animal diseases. The compounds of the present invention are useful for modulating or inhibiting PTP1B and/or TC-PTP and/or other PTPases showing key structural features with said PTPases and for treating diseases in which said modulation or inhibition is indicated. A few examples that are not intended in any way to limit the scope of the invention of substrates that may be regulated by PTP1B will be given below.

Tonks and coworkers have developed an elegant 'substrate trapping' technique that has allowed identification of the epidermal growth factor receptor (EGF-R) as a major substrate of PTP1B in COS cells (Flint *et al. Proc. Natl. Acad. Sci. USA 94:* 1680-1685 (1997)). In addition, three other as yet unidentified substrates of PTP1B were isolated. As an example of these studies, it has recently been found - using the above substrate-trapping technique - that PTP1B in addition to the EGF-R associates with activated platelet-derived growth factor

receptor (PDGF-R), but not with colony-stimulating factor 1 receptor (CSF-1R) (Liu & Chernoff, *Biochem. J. 327:* 139-145 (1997)).

Early studies have shown that the subcellular localization as well as the enzyme activity of PTP1B may be regulated by agonist-induced calpain-catalyzed cleavage in human platelets (Frangioni *et al. EMBO J. 12:* 4843-4856 (1993)). Moreover, PTP1B cleavage correlated with the transaction from reversible to irreversible platelet aggregation. Thus, as a non-limiting example compounds of the present invention might be used to prevent or induce irreversible platelet aggregation in individuals in need thereof. It was proposed that the cleavage-induced change in the subcellular localization of PTP1B (from membrane to cytosol) results in different substrate specificity not only in platelet but also in other cell types (Frangioni *et al.*, supra).

The above substrate trapping method has further been used to identify the protein tyrosine kinase $p210^{bcr\text{-}abl}$ as a substrate for PTP1B (LaMontagne, Jr. *et al. Mol. Cell. Biol. 18:* 2965-2975 (1998)). These studies suggest that PTP1B might function as a negative regulator of $p210^{bcr\text{-}abl}$ signaling *in vivo*. In addition, PTP1B was recently found to bind to and dephosphorylate the docting protein $p130^{Casin\ 341}$ rat fibroblasts and thereby suppress transformation by v-crk, v-src, and v-ras, but not by v-raf (Liu *et al. Mol. Cell. Biol. 18:* 250-259 (1998)).

The transmembrane PTPase CD45, which is believed to be hematopoietic cell-specific, was in a recent study found to negatively regulate the insulin receptor tyrosine kinase in the human multiple myeloma cell line U266 (Kulas *et al., J. Biol. Chem. 271*: 755-760 (1996)).

Further, PTPases influences the following hormones or diseases or disease states: somatostatin, the immune system/autoimmunity, cell-cell interactions/cancer, platelet aggregation, osteoporosis, and microorganisms, as disclosed in PCT Publication WO 99/15529 .

Somatostatin inhibits several biological functions including cellular proliferation (Lamberts *et al., Molec. Endocrinol. 8*: 1289-1297 (1994)). While part of the antiproliferative activities of somatostatin are secondary to its inhibition of hormone and growth factor secretion (e.g. growth hormone and epidermal growth factor), other antiproliferative effects of somatostatin are due to a direct effect on the target cells. As an example, somatostatin analogs inhibit the growth of pancreatic cancer presumably via stimulation of a single PTPase, or a subset of PTPases, rather than a general activation of PTPase levels in the cells (Liebow *et al., Proc. Natl. Acad. Sci. USA 86*: 2003-2007 (1989); Colas *et al., Eur. J. Biochem. 207*: 1017-1024 (1992)). In a recent study it was found that somatostatin stimulation of somatostatin receptors SSTR1, but not SSTR2, stably expressed in CHO-K1 cells can stimulate PTPase activity and that this stimulation is pertussis toxin-sensitive. Whether the inhibitory effect of somatostatin on hormone and growth factor secretion is caused by a similar stimulation of PTPase activity in hormone producing cells remains to be determined.

PTPases: the immune system/autoimmunity

Several studies suggest that the receptor-type PTPase CD45 plays a critical role not only for initiation of T cell activation, but also for maintaining the T cell receptor-mediated signaling cascade. These studies are reviewed in: (Weiss A., *Ann. Rev. Genet. 25*: 487-510 (1991); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Trowbridge and Thomas, *Annu. Rev. Immunol. 12*: 85-116 (1994)).

CD45 is one of the most abundant of the cell surface glycoproteins and is expressed exclusively on hemopoetic cells. In T cells, it has been shown that CD45 is one of the critical components of the signal transduction machinery of lymphocytes. In particular, evidence has suggested that CD45 phosphatase plays a pivotal role in antigen-

stimulated proliferation of T lymphocytes after an antigen has bound to the T cell receptor (Trowbridge, *Ann. Rev. Immunol*, 12: 85-116 (1994)). Several studies suggest that the PTPase activity of CD45 plays a role in the activation of Lck, a lymphocyte-specific member of the Src family protein-tyrosine kinase (Mustelin etal., *Proc. Natl. Acad. Sci. USA 86*: 6302-6306 (1989); Ostergaard *et al., Proc. Natl. Acad. Sci. USA 86*: 8959-8963 (1989)). These authors hypothesized that the phosphatase activity of CD45 activates Lck by dephosphorylation of a C-terminal tyrosine residue, which may, in turn, be related to T-cell activation. In a recent study it was found that recombinant p56lck specifically associates with recombinant CD45 cytoplasmic domain protein, but not to the cytoplasmic domain of the related PTPa (Ng et al., *J. Biol. Chem. 271*: 1295-1300 (1996)). The p56lck-CD45 interaction seems to be mediated via a nonconventional SH2 domain interaction not requiring phosphotyrosine. In immature B cells, another member of the Src family protein-tyrosine kinases, Fyn, seems to be a selective substrate for CD45 compared to Lck and Syk (Katagiri et al., *J. Biol. Chem. 270*: 27987-27990 (1995)).

Studies using transgenic mice with a mutation for the CD45-exon6 exhibited lacked mature T cells. These mice did not respond to an antigenic challenge with the typical T cell mediated response (Kishihara *et al.*, *Cell 74*:143-56 (1993)). Inhibitors of CD45 phosphatase would therefore be very effective therapeutic agents in conditions that are associated with autoimmune disease.

CD45 has also been shown to be essential for the antibody mediated degranulation of mast cells (Berger *et* al., *J. Exp. Med. 180*:471-6 (1994)). These studies were also done with mice that were CD45-deficient. In this case, an IgE-mediated degranulation was demonstrated in wild type but not CD45-deficient T cells from mice. These data suggest that CD45 inhibitors could also play a role in the symptomatic or therapeutic treatment of allergic disorders.

Another recently discovered PTPase, an inducible lymphoid-specific protein tyrosine phosphatase (HePTP) has also been implicated

in the immune response. This phosphatase is expressed in both resting T and B lymphocytes, but not non-hemopoetic cells. Upon stimulation of these cells, mRNA levels from the HePTP gene increase 10-15 fold (Zanke *et al.*, *Eur. J. Immunol. 22*: 235-239 (1992)). In both T and B cells HePTP may function during sustained stimulation to modulate the immune response through dephosphorylation of specific residues. Its exact role, however remains to be defined.

Likewise, the hematopoietic cell specific SHP-1 seems to act as a negative regulator and play an essential role in immune cell development.In accordance with the above-mentioned important function of CD45, HePTP and SHP-1, selective PTPase inhibitors may be attractive drug candidates both as immunosuppressors and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the vanadium-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven *et al.*, *J. Biol. Chem. 270*: 20824-20831 (1995)).

PTPases: cell-cell interactions/cancer

Focal adhesion plaques, an *in vitro* phenomenon in which specific contact points are formed when fibroblasts grow on appropriate substrates, seem to mimic, at least in part, cells and their natural surroundings. Several focal adhesion proteins are phosphorylated on tyrosine residues when fibroblasts adhere to and spread on extracellular matrix (Gumbiner, *Neuron 11:* 551-564 (1993)). However, aberrant tyrosine phosphorylation of these proteins can lead to cellular transformation. The intimate association between PTPases and focal adhesions is supported by the finding of several intracellular PTPases with ezrin-like N-terminal domains, e.g. PTPMEG1 (Gu *et al., Proc. Natl. Acad. Sci. USA 88*: 5867-5871 (1991), PTPH1 (Yang and Tonks,

Proc. Natl. Acad. Sci. USA 88: 5949-5953 (1991)) and PTPD1 (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)). The ezrin-like domain show similarity to several proteins that are believed to act as links between the cell membrane and the cytoskeleton. PTPD1 was found to be phosphorylated by and associated with c-src *in vitro* and is hypothesized to be involved in the regulation of phosphorylation of focal adhesions (Møller *et al.*, *supra*).

PTPases may oppose the action of tyrosine kinases, including those responsible for phosphorylation of focal adhesion proteins, and may therefore function as natural inhibitors of transformation. TC-PTP, and especially the truncated form of this enzyme (Cool *et al., Proc. Natl. Acad. Sci. USA 87:* 7280-7284 (1990)), can inhibit the transforming activity of v-*erb* and v-*fms* (Lammers *et al., J. Biol. Chem. 268:* 22456-22462 (1993), Zander *et al., Oncogene 8:* 1175-1182 (1993)). Moreover, it was found that transformation by the oncogenic form of the *HER2/neu* gene was suppressed in NIH 3T3 fribroblasts overexpressing PTP1B (Brown-Shimer *et al., Cancer Res. 52:* 478-482 (1992)).

The expression level of PTP1B was found to be increased in a mammary cell line transformed with *neu* (Zhay *et al., Cancer Res. 53:* 2272-2278 (1993)). The intimate relationship between tyrosine kinases and PTPases in the development of cancer is further evidenced by the recent finding that PTPe is highly expressed in murine mammary tumors in transgenic mice over-expressing c-*neu* and v-Ha-*ras*, but not c-*myc* or *int-2* (Elson and Leder, *J. Biol. Chem. 270:* 26116-26122 (1995)). Further, the human gene encoding PTPγ was mapped to 3p21, a chromosomal region which is frequently deleted in renal and lung carcinomas (LaForgia *et al., Proc. Natl. Acad. Sci. USA 88*: 5036-5040 (1991)).

In this context, it seems significant that PTPases appear to be involved in controlling the growth of fibroblasts. In a recent study it was found that Swiss 3T3 cells harvested at high density contain a

membrane-associated PTPase whose activity on an average is 8-fold higher than that of cells harvested at low or medium density (Pallen and Tong, *Proc. Natl. Acad. Sci. USA 88*: 6996-7000 (1991)). It was hypothesized by the authors that density-dependent inhibition of cell growth involves the regulated elevation of the activity of the PTPase(s) in question. In accordance with this view, a novel membrane-bound, receptor-type PTPase, DEP-1, showed enhanced (>=10-fold) expression levels with increasing cell density of WI-38 human embryonic lung fibroblasts and in the AG1518 fibroblast cell line (Östman *et al., Proc. Natl. Acad. Sci. USA 91*: 9680-9684 (1994)).

Two closely related receptor-type PTPases, PTPκ and PTPμ, can mediate homophilic cell-cell interaction when expressed in non-adherent insect cells, suggesting that these PTPases might have a normal physiological function in cell-to-cell signalling (Gebbink *et al., J. Biol. Chem. 268*: 16101-16104 (1993), Brady-Kalnay *et al., J. Cell Biol. 122*: 961-972 (1993); Sap *et al., Mol. Cell. Biol. 14*: 1-9 (1994)). Interestingly, PTPk and PTPμ do not interact with each other, despite their structural similarity (Zondag *et al., J. Biol. Chem. 270*: 14247-14250 (1995)). From the studies described above it is apparent that PTPases may play an important role in regulating normal cell growth. However, as pointed out above, recent studies indicate that PTPases may also function as positive mediators of intracellular signaling and thereby induce or enhance mitogenic responses. Increased activity of certain PTPases might therefore result in cellular transformation and tumor formation. Indeed, in one study over-expression of PTPα was found to lead to transformation of rat embryo fibroblasts (Zheng, *supra*). In addition, a novel PTP, SAP-1, was found to be highly expressed in pancreatic and colorectal cancer cells. SAP-1 is mapped to chromosome 19 region q13.4 and might be related to carcinoembryonic antigen mapped to 19q13.2 (Uchida *et al., J. Biol. Chem. 269*: 12220-12228 (1994)). Further, the dsPTPase, cdc25, dephosphorylates cdc2 at Thr14/Tyr-15 and thereby functions as positive regulator of

mitosis (reviewed by Hunter, *Cell 80*: 225-236 (1995)). Inhibitors of specific PTPases are therefore likely to be of significant therapeutic value in the treatment of certain forms of cancer.

PTPases: platelet aggregation

PTPases seem to be centrally involved in platelet aggregation. Thus, agonist-induced platelet activation results in calpain-catalyzed cleavage of PTP1B with a concomitant 2-fold stimulation of PTPase activity (Frangioni *et al., EMBO J. 12:* 4843-4856 (1993)). The cleavage of PTP1B leads to subcellular relocation of the enzyme and correlates with the transition from reversible to irreversible platelet aggregation in platelet-rich plasma. In addition, the SH2 domain containing PTPase, SHP-1, was found to translocate to the cytoskeleton in platelets after thrombin stimulation in an aggregation-dependent manner (Li *et al., FEBS Lett. 343:* 89-93 (1994)).

Although some details in the above two studies have been questioned, there is over-all agreement that PTP1B and SHP-1 play significant functional roles in platelet aggregation (Ezumi *et al., J. Biol. Chem. 270:* 11927-11934 (1995)). In accordance with these observations, treatment of platelets with the PTPase inhibitor pervanadate leads to significant increase in tyrosine phosphorylation, secretion and aggregation (Pumiglia *et al., Biochem. J. 286:* 441-449 (1992)).

PTPases: osteoporosis

The rate of bone formation is determined by the number and the activity of osteoblasts, which in term are determined by the rate of proliferation and differentiation of osteoblast progenitor cells, respectively. Histomorphometric studies indicate that the osteoblast number is the primary determinant of the rate of bone formation in humans (Gruber *et*

al., Mineral Electrolyte Metab. 12: 246-254 (1987), reviewed in Lau *et al., Biochem. J. 257*: 23-36 (1989)). Acid phosphatases/PTPases may be involved in negative regulation of osteoblast proliferation. Thus, fluoride, which has phosphatase inhibitory activity, has been found to increase spinal bone density in osteoporotics by increasing osteoblast proliferation (Lau *et al., supra*). Consistent with this observation, an osteoblastic acid phosphatase with PTPase activity was found to be highly sensitive to mitogenic concentrations of fluoride (Lau *et al., J. Biol. Chem. 260*: 4653-4660 (1985), Lau *et al., J. Biol. Chem. 262*: 1389-1397 (1987), Lau *et al., Adv. Protein Phosphatases 4*: 165-198 (1987)). Interestingly, it was recently found that the level of membrane-bound PTPase activity was increased dramatically when the osteoblast-like cell line UMR 106.06 was grown on collagen type-I matrix compared to uncoated tissue culture plates. Since a significant increase in PTPase activity was observed in density-dependent growth arrested fibroblasts (Pallen and Tong, *Proc. Natl. Acad. Sci. 88*: 6996-7000 (1991)), it might be speculated that the increased PTPase activity directly inhibits cell growth. The mitogenic action of fluoride and other phosphatase inhibitors (molybdate and vanadate) may thus be explained by their inhibition of acid phosphatases/PTPases that negatively regulate the cell proliferation of osteoblasts. The complex nature of the involvement of PTPases in bone formation is further suggested by the recent identification of a novel parathyroid regulated, receptor-like PTPase, OST-PTP, expressed in bone and testis (Mauro *et al., J. Biol. Chem. 269*: 30659-30667 (1994)). OST-PTP is up-regulated following differentiation and matrix formation of primary osteoblasts and subsequently down-regulated in the osteoblasts which are actively mineralizing bone in culture. It may be hypothesized that PTPase inhibitors may prevent differentiation via inhibition of OST-PTP or other PTPases thereby leading to continued proliferation. This would be in agreement with the above-mentioned effects of fluoride and the observation that the tyrosine phosphatase inhibitor orthovanadate

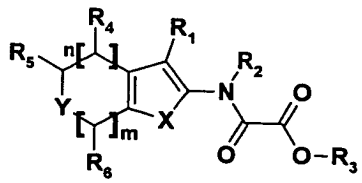
appears to enhance osteoblast proliferation and matrix formation (Lau *et al., Endocrinology 116*: 2463-2468 (1988)). In addition, it was recently observed that vanadate, vanadyl and pervanadate all increased the growth of the osteoblast-like cell line UMR106. Vanadyl and pervanadate were stronger stimulators of cell growth than vanadate. Only vanadate was able to regulate the cell differentiation as measured by cell alkaline phosphatase activity (Cortizo *et al., Mol. Cell. Biochem. 145*: 97-102 (1995)).

PTPases: microorganisms

Dixon and coworkers have called attention to the fact that PTPases may be a key element in the pathogenic properties of *Yersinia* (reviewed in Clemens *et al. Molecular Microbiology 5*: 2617-2620 (1991)). This finding was rather surprising since tyrosine phosphate is thought to be absent in bacteria. The genus *Yersinia* comprises 3 species: *Y. pestis* (responsible for the bubonic plague), *Y. pseudoturberculosis* and *Y. enterocolitica* (causing enteritis and mesenteric lymphadenitis). Interestingly, a dual-specificity phosphatase, VH1, has been identified in Vaccinia virus (Guan *et al., Nature 350*: 359-263 (1991)). These observations indicate that PTPases may play critical roles in microbial and parasitic infections, and they further point to PTPase inhibitors as a novel, putative treatment principle of infectious diseases.

DESCRIPTION OF THE INVENTION

The present invention relates to Compounds of the Formula 1 wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined below;



Formula 1

In the above Formula 1

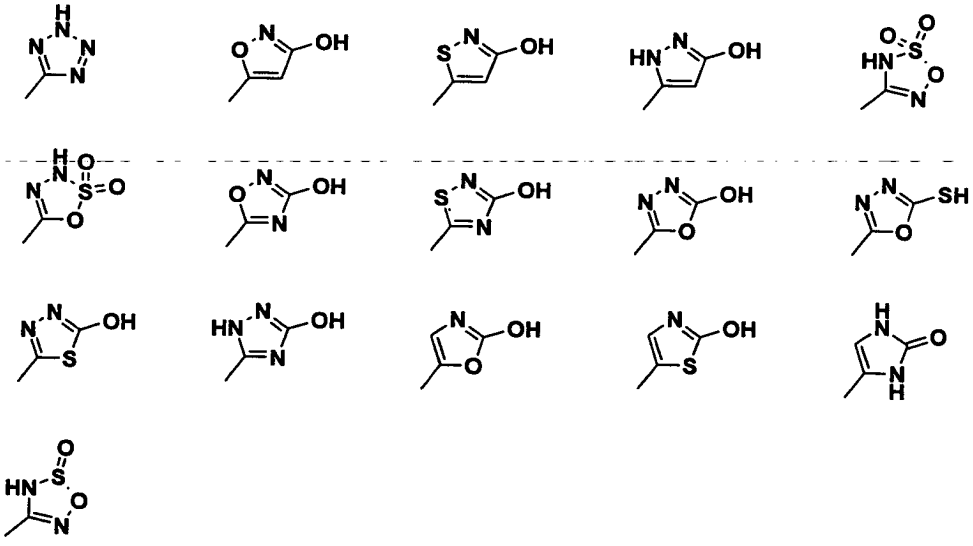
n is 0, 1 or 2;

m is 1 or 2;

X is S, O, NR_7;

Y is O, S, SO, SO_2;

R_1 is hydrogen, $COOR_3$, or selected from the following 5-membered heterocycles:



R_2 is hydrogen, C_1-C_6alkyl, hydroxy, NR_7R_8;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonyl-amino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl-$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, C_1-C_6alkylamino-C_1-C_6alkyl or NR_9R_{10}, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

The compounds of the invention can be further modified to act as prodrugs.

It is a well known problem in drug discovery that compounds, such as enzyme inhibitors, may be very potent and selective in biochemical assays, yet be inactive in vivo. This lack of so-called bioavailability may be ascribed to a number of different factors such as lack of or poor absorption in the gut, first pass metabolism in the liver, poor uptake in cells. Although the factors determining bioavailability are not completely understood, there are many examples in the scientific literature - well known to those skilled in the art - of how to modify compounds, which are potent and selective in biochemical assays but show low or no activity in vivo, into drugs that are biologically active. It is within the scope of the invention to modify the compounds of the invention, termed the 'original compound', by attaching chemical groups that will improve the bioavailability of said compounds in such a way that the uptake in cells or mammals is facilitated. Examples of said modifications, which are not intended in any way to limit the scope of the invention, include changing of one or more carboxy groups to esters (for instance methyl esters, ethyl esters, acetoxymethyl esters or other acyloxymethyl esters). Compounds of the invention, original compounds, such modified by attaching chemical groups are termed 'modified compounds'. Said chemical groups may or may not be apparent in the claims of this invention. Other examples of modified compounds, which are not intended in any way to limit the scope of the invention, are compounds that have been cyclized at specific positions - socalled 'cyclic compounds' - which upon uptake in cells or

mammals become hydrolyzed at the same specific position(s) in the molecule to yield the compounds of the invention, the original compounds, which are then said to be 'non-cyclic'. For the avoidance of doubt, it is understood that the latter original compounds in most cases will contain other cyclic or heterocyclic structures that will not be hydrolyzed after uptake in cells or mammals. Generally, said modified compounds will not show a behavior in biochemical assays similar to that of the original compound, i.e. the corresponding compounds of the invention without the attached chemical groups or said modifications. Said modified compounds may even be inactive in biochemical assays. However, after uptake in cells or mammals these attached chemical groups of the modified compounds may in turn be removed spontaneously or by endogenous enzymes or enzyme systems to yield compounds of the invention, original compounds. 'Uptake' is defined as any process that will lead to a substantial concentration of the compound inside cells or in mammals. After uptake in cells or mammals and after removal of said attached chemical group or hydrolysis of said cyclic compound, the compounds may have the same structure as the original compounds and thereby regain their activity and hence become active in cells and/or in vivo after uptake. A number of procedures, well known to those skilled in the art, may be used to verify that the attached chemical groups have been removed or that the cyclic compound has been hydrolyzed after uptake in cells or mammals. An example, which is not intended in any way to limit the scope of the invention, is given in the following. A mammalian cell line, which can be obtained from the American Tissue Type Collection or other similar governmental or commercial sources, is incubated with said modified compound. After incubation at conditions well known to those skilled in the art, the cells are washed appropriately, lysed and the lysate is isolated. Appropriate controls, well known to those skilled in the art, must be included. A number of different procedures, well known to those skilled in the art, may in turn be used to extract and purify said compound from said lysate. Said compound may or may not retain the attached

chemical group or said cyclic compound may or may not have been hydrolyzed. Similarly, a number of different procedures - well known to those skilled in the art - may be used to structurally and chemically characterize said purified compound. Since said purified compound has been isolated from said cell lysate and hence has been taken up by said cell line, a comparison of said structurally and chemically characterized compound with that of the original unmodified compound (i.e. without said attached chemical group or said non-cyclic compound) will immediately provide those skilled in the art information on whether the attached chemical group as been removed in the cell or if the cyclic compound has been hydrolyzed. As a further analysis, said purified compound may be subjected to enzyme kinetic analysis as described in detail in the present invention. If the kinetic profile is similar to that of the original compound without said attached chemical group, but different from said modified compound, this confirms that said chemical group has been removed or said cyclic compounds has been hydrolyzed.Similar techniques may be used to analyze compounds of the invention in whole animals and mammals.

A preferred prodrug is acetoxymethyl esters of the compounds of the present invention which may be prepared by the following general procedure *(C.Schultz et al, The Journal of Biological Chemistry,* **1993**, *268,* 6316-6322.*)*:

A carboxylic acid (1 equivalent) is suspended in dry acetonitrile (2 ml per 0.1 mmol). Diisopropyl amine (3.0 equivalents) is added followed by bromomethyl acetate (1.5 equivalents). The mixture is stirred under nitrogen overnight at room temperature. Acetonitrile is removed under reduced pressure to yield an oil which is diluted in ethyl acetate and washed with water (3 x). The organic layer is dried over anhydrous magnesium sulfate. Filtration followed by solvent removal under reduced

pressure afford a crude oil. The product is purified by column chromatography on silica gel, using an appropriate solvent system.

DEFINITIONS

As used herein, the term "attached" or "-" (e.g. -COR_{11} which indicates the carbonyl attachment point to the scaffold) signifies a stable covalent bond, certain preferred points of attachment points being apparent to those skilled in the art.

The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes C_1-C_6 straight chain saturated, methylene and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_1-C_6 branched saturated and C_2-C_6 unsaturated aliphatic hydrocarbon groups, C_3-C_6 cyclic saturated and C_5-C_6 unsaturated aliphatic hydrocarbon groups, and C_1-C_6 straight chain or branched saturated and C_2-C_6 straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_6 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, and the like.

The term "substituted alkyl" represents an alkyl group as defined above wherein the substitutents are independently selected from halo, cyano, nitro, trihalomethyl, carbamoyl, hydroxy, oxo, $COOR_3$, $CONR_7R_8$, C_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, thio, C_1-C_6alkylthio, arylthio, arylC_1-C_6alkylthio, NR_7R_8, C_1-C_6alkylamino, arylamino, arylC_1-C_6alkylamino, di(arylC_1-C_6alkyl)amino, C_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonyl, C_1-C_6alkylcarboxy, arylcarboxy, arylC_1-C_6alkylcarboxy, C_1-

C_6alkylcarbonyl-amino, -C_1-C_6alkylaminoCOR_{12}, arylC_1-C_6alkylcarbonyl-amino, tetrahydrofuranyl, morpholinyl, piperazinyl, -CONR_7R_8, -C_1-C_6alkylCONR_7R_8, or a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam; wherein R_{11} is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy and R_3 is defined as above or NR_7R_8, wherein R_7, R_8 are defined as above.

The term "saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system" represents but are not limit to aziridinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, indolyl, isoindolyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinoxalinyl, indolinyl, indazolyl, benzimidazolyl, benzotriazolyl, purinyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, iminodibenzyl, iminostilbenyl.
The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through an oxygen bridge.
The term "alkyloxyalkyl" represents an "alkyloxy" group attached through an alkyl group as defined above having the indicated number of carbon atoms.
The term "alkyloxyalkyloxy" represents an "alkyloxyalkyl" group attached through an oxygen atom as defined above having the indicated number of carbon atoms.

The term "aryloxy" (e.g. phenoxy, naphthyloxy and the like) represents an aryl group as defined below attached through an oxygen bridge.
The term "arylalkyloxy" (e.g. phenethyloxy, naphthylmethyloxy and the like) represents an "arylalkyl" group as defined below attached through an oxygen bridge.

The term "arylalkyloxyalkyl" represents an "arylalkyloxy" group as defined above attached through an "alkyl" group defined above having the indicated number of carbon atoms.

The term "arylthio" (e.g. phenylthio, naphthylthio and the like) represents an "aryl" group as defined below attached through an sulfur bridge.

The term "alkyloxycarbonyl" (e.g. methylformiat, ethylformiat and the like) represents an "alkyloxy" group as defined above attached through a carbonyl group.

The term "aryloxycarbonyl" (e.g. phenylformiat, 2-thiazolylformiat and the like) represents an "aryloxy" group as defined above attached through a carbonyl group.

The term "arylalkyloxycarbonyl" (e.g. benzylformiat, phenyletylformiat and the like) represents an "arylalkyloxy" group as defined above attached through a carbonyl group.

The term "alkyloxycarbonylalkyl" represents an "alkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkyloxycarbonylalkyl" represents an "arylalkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the like) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "arylalkylthio" (e.g. phenylmethylthio, phenylethylthio, and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "alkylthioalkyl" represents an "alkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylthioalkyl" represents an "arylalkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-hexylamino, (2-cyclopentyl)propylamino, hexenylamino, pyrrolidinyl, piperidinyl and the like) represents one or two "alkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_7R_8, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_7 and R_8 are defined as above.

The term "arylalkylamino" (e.g. benzylamino, diphenylethylamino and the like) represents one or two "arylalkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two "arylalkyl" groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_7R_8, C_1-C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_7 and R_8 are defined as above.

The term "alkylaminoalkyl" represents an "alkylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylaminoalkyl" represents an "arylalkylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkyl" (e.g. benzyl, phenylethyl) represents an "aryl" group as defined below attached through an alkyl having the indicated number of carbon atoms or substituted alkyl group as defined above.

The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "arylcarbonyl" (benzoyl) represents an "aryl" group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. phenylcyclopropylcarbonyl, phenylethylcarbonyl and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "alkylcarbonylalkyl" represents an "alkylcarbonyl" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarbonylalkyl" represents an "arylalkylcarbonyl" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term "arylcarboxyalkyl" (e.g. phenylcarboxymethyl) represents an "arylcarbonyl" group defined above wherein the carbonyl is in turn attached through an oxygen bridge to an alkyl chain having the indicated number of carbon atoms.

The term "arylalkylcarboxy" (e.g. benzylcarboxy, phenylcyclopropylcarboxy and the like) represents an "arylalkylcarbonyl"

group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term "alkylcarboxyalkyl" represents an "alkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarboxyalkyl" represents an "arylalkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylamino" (e.g. benzylcarbonylamino and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkyl" represents an "alkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylaminoalkyl" represents an "arylalkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkylcarbonyl" represents an alkylcarbonylaminoalkyl group attached through a carbonyl group. The nitrogen atom may be further substituted with an "alkyl" or "aryl" group.

The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently

attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, $COOR_3$, $CONR_7R_8$, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_7R_8, C_1-C_6-alkylamino, C_1-C_6alkylaminoC_1-C_6alkyl, arylamino, arylC_1-C_6alkylamino, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, carboxyC_1-C_6-alkyloxy, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6-alkylcarbonylaminoC_1-C_6alkyl, $-CONR_7R_8$, or -C_1-C_6alkyl$CONR_7R_8$; wherein R_3, R_7, R_8, and R_{11} are defined as above and the alkyl and aryl groups are optionally substituted as defined in the definition section;

The definition of aryl includes but is not limited to phenyl, biphenyl, indenyl, fluorenyl, naphthyl (1-naphthyl, 2-naphthyl), pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiophenyl (2-thiophenyl, 3-thiophenyl, 4-thiophenyl, 5-thiophenyl), furanyl (2-furanyl, 3-furanyl, 4-furanyl, 5-furanyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl), 5-tetrazolyl, pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-

isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo-[b]furanyl), 6-(2,3-dihydro-benzo-[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]-thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]-thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]-thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]-thiophenyl)), 4,5,6,7-tetrahydro-benzo[b]thiophenyl (2-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 3-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 4-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 5-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 6-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 7-(4,5,6,7-tetrahydro-benzo[b]thiophenyl)), 4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl (4-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 5-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 6-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 7-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl)), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl (1-isoindolyl, 2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), 1,3-dihydro-isoindolyl (1-(1,3-dihydro-isoindolyl), 2-(1,3-dihydro-isoindolyl), 3-(1,3-dihydro-isoindolyl), 4-(1,3-dihydro-isoindolyl), 5-(1,3-dihydro-isoindolyl), 6-(1,3-dihydro-isoindolyl), 7-(1,3-dihydro-isoindolyl)), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benz-oxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzo-thiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz-[b,f]azepine-2-yl,

5H-dibenz[b,f]azepine-3-yl, 5H-dibenz-[b,f]azepine-4-yl, 5H-dibenz[b,f]-azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz-[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), pyrrolidinyl (1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl), phenylpyridyl (2-phenyl-pyridyl, 3-phenyl-pyridyl, 4-phenylpyridyl), phenylpyrimidinyl (2-phenylpyrimidinyl, 4-phenyl-pyrimidinyl, 5-phenylpyrimidinyl, 6-phenylpyrimidinyl), phenylpyrazinyl, phenylpyridazinyl (3-phenylpyridazinyl, 4-phenylpyridazinyl, 5-phenyl-pyridazinyl).

The term "arylcarbonyl" (e.g. 2-thiophenylcarbonyl, 3-methoxy-anthrylcarbonyl, oxazolylcarbonyl) represents an "aryl" group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)propylcarbonyl, (2-chloronaphthyl)pentenylcarbonyl, imidazolylcyclopentylcarbonyl) represents an "arylalkyl" group as defined above wherein the "alkyl" group is in turn attached through a carbonyl.

The compounds of the present invention have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

Pharmaceutically acceptable salts of the Compounds of Formula 1, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as -COOH, 5-tetrazolyl or $-P(O)(OH)_2$, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate,

citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethane sulfonate, picrate and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, can be used as the dosage form.

Also, in the case of the -COOH or $-P(O)(OH)_2$ being present, pharmaceutically acceptable esters can be employed, e.g., methyl, tert-butyl, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

In a preferred embodiment of the invention X in formula 1 is sulphur and Y is oxygen.

In another preferred embodiment of the invention R_1 is $COOR_3$ and R_2 is hydrogen; wherein R_3 is hydrogen, C_1-C_6alkyl or arylC_1-C_6alkyl.

In a further preferred embodiment of the invention n and m are 1.

In a further preferred embodiment of the invention R_4 and R_6 are both hydrogen and R_5 is $CONR_7R_8$, wherein R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl or aryl.

Most preferred is R_7 hydrogen and R_8 is phenyl or benzyl.

In a further preferred embodiment of the invention R_4 and R_6 are both hydrogen and R_5 is C_1-C_6alkylNR_7R_8, wherein R_7 and R_8 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system being optionally substituted as defined above.

Preferably are R_8 and R_9 together with the nitrogen to which they are attached forming an isoindol, thiazolidine, pyrrolopyrazine, pyrrolopyridine, benzo[d]isoxazol, 1,3-dihydro-benzo[d]isothiazol or 1,1-dioxo-1,3-dihydro-benzo[d]isothiazol ring, the ring system being optionally substituted as defined above.

Most preferred ring systems are 1,3-dihydro-benzo[d]isothiazol or 1,1-dioxo-1,3-dihydro-benzo[d]isothiazol rings.

In a further preferred embodiment of the invention R_4 and R_5 are both hydrogen and R_6 is $CONR_7R_8$, wherein R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl or aryl.

Most preferred is R_7 hydrogen and R_8 is phenyl or benzyl.

In a further preferred embodiment of the invention R_4 and R_5 are both hydrogen and R_6 is C_1-C_6alkylNR_7R_8, wherein R_7 and R_8 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system being optionally substituted as defined above.

Preferably are R_8 and R_9 together with the nitrogen to which they are attached forming an isoindol, thiazolidine, pyrrolopyrazine or pyrrolopyridine, benzo[d]isoxazol, 1,3-dihydro-benzo[d]isothiazol or 1,1-dioxo-1,3-dihydro-benzo[d]isothiazol ring, the ring system being optionally substituted as defined above.

Most preferred ring systems are 1,3-dihydro-benzo[d]isothiazol and 1,1-dioxo-1,3-dihydro-benzo[d]isothiazol rings.

The following compounds are preferred:

5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester methyl ester;

Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester;

7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester;

7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-[4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[3-(2,4-Dimethoxy-phenyl)-ureidomethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)-carbamoyl)-nicotinic acid;

5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[(2-Amino-3-phenyl-propionylamino)-methyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid and
2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid.

PHARMACOLOGICAL METHODS

The compounds are evaluated for biological activity with a truncated form of PTP1B (corresponding to the first 321 amino acids), which was expressed in E. coli and purified to apparent homogeneity using published procedures well-known to those skilled in the art. The enzyme reactions are carried out using standard conditions essentially as described by Burke et al. (*Biochemistry* **35**; 15989-15996 (1996)). The assay conditions are as follows. Appropriate concentrations of the compounds of the invention are added to the reaction mixtures containing different concentrations of the substrate, *p*-nitrophenyl phosphate (range: 0.16 to 10 mM - final assay concentration). The buffer used was 100 mM sodium acetate pH 5.5, 50 mM sodium chloride, 0.1 % (w/v) bovine serum albumin and 5 mM dithiothreitol (total volume 100 ml). The reaction was started by addition of the enzyme and carried out in microtiter plates at 25° C for 60 minutes. The reactions are stopped by addition of NaOH. The enzyme activity was determined by measurement of the absorbance at 405 nm with appropriate corrections for absorbance at 405 nm of the compounds and *p*-nitrophenyl phosphate. The data are analyzed using nonlinear regression fit to classical Michaelis Menten enzyme kinetic models. Inhibition is expressed as K_i values in μM. The results of representative experiments are shown in Table 1

Table 1

Inhibition of classical PTP1B by compounds

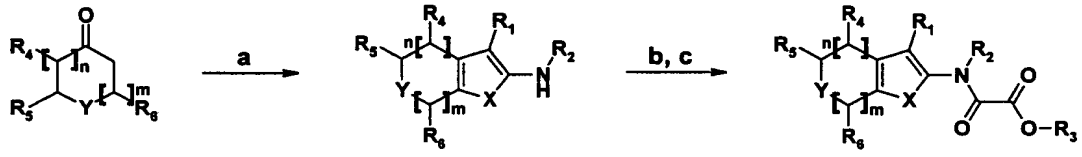
of the invention

Example no.	PTP1B K_i values (μM)
46	0.8

THE SYNTHESIS OF THE COMPOUNDS

In accordance with one aspect of the invention, the compounds of the invention are prepared as illustrated in the following reaction scheme:

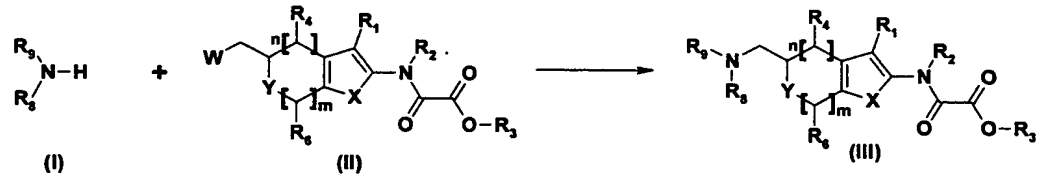
Method A



a) $NCCH_2COOR_3$, sulphur, morpholine or triethylamine, EtOH; b) $R_3OCOCOimidazole$, THF; c) 25 % TFA/CH_2Cl_2; wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5, and R_6 are defined above;

When R_4 is hydrogen the reaction step a) in Method A gives a mixture of regioisomers which can be separated by use of column chromatography known to thus skilled in the art.

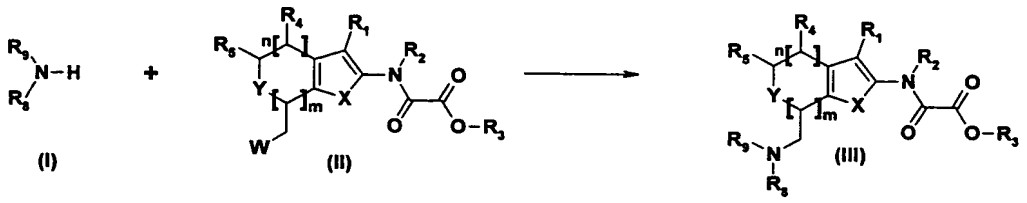
Method B



(I) (II) (III)

By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, *Synthesis*, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, Y, R_1, R_2, R_3, R_4, R_6, R_8 and R_9 are defined above.

Method C



(I) (II) (III)

By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, *Synthesis*, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, Y, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are defined above.

Pharmacological Preparations

For the above indications the dosage will vary depending on the compound of the invention employed, on the mode of administration and on the therapy desired. However, in general, satisfactory results are obtained with a dosage of from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg of compounds of the invention, conveniently given from 1 to 5 times daily, optionally in sustained release form. Usually, dosage forms suitable for oral administration comprise from about 0.5 mg to about 1000 mg, preferably from about 1 mg to about 500 mg of the compounds of the invention admixed with a pharmaceutical carrier or diluent.

The compounds of the invention may be administered in a pharmaceutically acceptable acid addition salt form or where possible as a metal or a C_{1-6}-alkylammonium salt. Such salt forms exhibit approximately the same order of activity as the free acid forms.

This invention also relates to pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and, usually, such compositions also contain a pharmaceutical carrier or diluent. The compositions containing the compounds of this invention may be prepared by conventional techniques and appear in conventional forms, for example capsules, tablets, solutions or suspensions.

The pharmaceutical carrier employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatine, agar, pectin, acacia, magnesium stearate and stearic acid. Examples of liquid carriers are syrup, peanut oil, olive oil and water.

Similarly, the carrier or diluent may include any time delay material known to the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier for oral administration is used, the preparation can be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Generally, the compounds of this invention are dispensed in unit dosage form comprising 10-200 mg of active ingredient in or together with a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-500 mg/day, e.g. about 100 mg per dose, when administered to patients, e.g. humans, as a drug.

A typical tablet that may be prepared by conventional tabletting techniques contains

Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Areosil®)	1.5 mg
Cellulose, microcryst. (Avicel®)	70 mg
Modified cellulose gum (Ac-Di-Sol®)	7.5 mg
Magnesium stearate	

Coating:

HPMC	approx.	9 mg
*Mywacett® 9-40 T	approx.	0.9 mg

*Acylated monoglyceride used as plasticiser for film coating.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intranasal, intramuscular, topical, intravenous, intraurethral, ophthalmic solution or an ointment, the oral route being preferred.

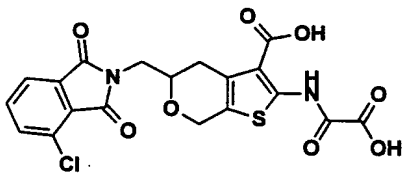
EXAMPLES

The process for preparing compounds of Formula 1 and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

Hereinafter, TLC is thin layer chromatography, $CDCl_3$ is deuterio chloroform, CD_3OD is tetradeuterio methanol and DMSO-d_6 is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^1H NMR shifts (δ_H) are given in parts per million (ppm) down field from tetramethylsilane as internal reference standard. M.p.: is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still *et al.*, *J. Org. Chem. 43:* 2923 (1978) on Merck silica gel 60 (Art. 9385). HPLC analyses are performed using 5μm C18 4 x 250 mm column eluted with various mixtures of water and acetonitrile, flow = 1 ml/min, as described in the experimental section.

Compounds used as starting material are either known compounds or compounds which can readily be prepared by methods known per se.

EXAMPLE 1



5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of benzyloxyacetaldehyde (8.3 g, 0.06 mol) in benzene (80 mL) was added 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (10.6 g, 0.06

mol). The reaction mixture was stirred under nitrogen for 15 min., cooled to 0 °C and a solution of 0.5 M zinc chloride (55 ml, 0.03 mol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 16 h and evaporated in vacuo. The resultant oil was diluted with ethyl acetate (100 ml), washed with 1N hydrochloric acid (3 x 50ml), saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$) and evaporated in vacuo. The resulting oil was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (1:2) as eluent. Pure fractions were collected affording after evaporation in vacuo 7.1 g (60 %) of benzyloxy-methyl-2,3-dihydro-pyran-4-one as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.31 (m, 6H), 5.42 (dd, J = 6,1 Hz, 1H), 4.61 (d, J = 3 Hz, 1H), 4,57 (m, 1H), 3.70 (m, 2H), 2.74 (dd, J = 17 Hz, 14 Hz, 1H), 2.41 (ddd, J = 17 Hz, 2 Hz, 1 Hz, 1H).

The above 2,3-dihydro-pyran-4-one (7.1 g, 0.032 mol) and 10 % palladium on carbon (0.4 g) in ethyl acetate (50 ml) were placed in a Parr bomb shaker and hydrogenated at 30 psi. The reaction mixture was shaken for 2 h, at which time TLC analysis (methanol/dichloromethane 1:9) indicated the reaction was complete. The reaction mixture was filtered through a pad of Celite and the volatiles evaporated in vacuo. The residue was subjected to flash column chromatography using ethyl acetate as eluent. Pure fractions were collected affording after evaporation in vacuo 3.0 g (75 %) of 2-hydroxymethyl-tetrahydro-pyran-4-one as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 - 4.29 (m, 1H), 3.77 - 3.66 (m, 3H), 3.61 - 3.54 (m, 1H), 2.65 - 2.43 (m, 2H), 2.34 - 2.27 (m, 2H), 2.04 (bs, 1H, CH_2OH).

The above tetrahydro-pyran-4-one (1.90 g, 0.015 mol), *tert*-butyl cyanoacetate (2.7 g, 0.019 mol), sulfur (0.51 g, 0.016 mol) and morpholine (2.55 ml, 0.03 mol) were dissolved in absolute ethanol (20 ml), and heated to 50 °C for 16 h. The reaction mixture was cooled, filtered and the filtrate evaporated in vacuo. The resultant oil was dissolved in ethyl acetate (50

ml), washed with water (2 x 50 ml), brine (2 x 50 m) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was subjected to flash column chromatography using ethyl acetate/hexanes (1:1) as eluent. Pure fractions were collected affording after evaporation in vacuo 3.7 g (90 %) of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (s, 2H), 3.80 - 3.67 (m, 3H), 2.77 - 2.72 (m, 1H), 2.57 - 2.53 (m, 1H), 1.54 (s, 9H).

The above carboxylic acid *tert*-butyl ester (1.0 g, 3.5 mmol), 4-chloro-1,3-dioxo-1,3-dihydro-isoindol (0.67 g, 3.7 mmol) and triphenylphosphine (1.01 g, 3.9 mmol) were dissolved in dry tetrahydrofuran (30 ml) and cooled to 0 °C under a nitrogen atmosphere. Diisopropyl azodicarboxylate (DIAD) (0.62 ml, 3.9 mmol) was added dropwise at 0 °C and the solution allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and the resultant solid dissolved in ethyl acetate (50 ml). The organic phase was washed with brine (3 x 50 ml), dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexanes (1:3) as eluent. Semi pure fractions were collected affording after evaporation in vacuo 0.7 g which was trituated with diethyl ether. The solid was filtered off and washed with diethyl ether and dried in vacuo affording 0.13 g (27 %) of 2-amino-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid. The filtrate was evaporated in vacuo. The residue (0.48 g) was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexanes (1:3) as eluent. Pure fractions were collected affording after evaporation in vacuo an additional 0.36 g (23 %) of 2-amino-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

To the above 4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert* butyl ester (0.36 g, 0.8 mmol) dissolved in tetrahydrofuran (20 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.31 g, 1.6 mmol) in tetrahydrofuran (3.4 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature for 18 hours. An additional portion of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (0.3 g, 1.6 mmol) in tetrahydrofuran (2 ml) was added. The reaction mixture was allowed to stir at room temperature for an additional 60 h. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with brine (3 x 50 ml) dried (Na_2SO_4), filtered and the organic phase evaporated in vacuo. The residue (0.5 g) was purified by column chromatography (300 ml silicagel) using a mixture of ethyl acetate/heptane (1:2) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.36 g (80 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

The above di-*tert*-butyl ester (0.3 g, 0.52 mmol) was dissolved in dichloromethane (1.2 ml) and trifluoroacetic acid (0.5 ml) was added. The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue trituated with a mixture of diethyl ether and heptane (1:1) (5 ml). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 200 mg (69 %) of the title compound as a solid.

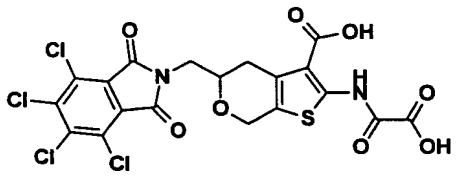
M.p.: > 250 °C

Calculated for $C_{19}H_{13}N_2ClO_8S$;

C, 49.09 %; H, 2.82 %; N, 6.03 %. Found:

C, 48.79 %; H, 2.79 %; N, 5.89 %.

EXAMPLE 2



5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4 ml scintillating vial, a solution of tetrachloro phthalimide (148 mg, 0.52 mmol) in N,N-dimethylformamide (2.0 ml) was heated to 100°C for 10 minutes and treated with potassium hydride (55 mg, 0.48 mmol, 35 % w/w dispersion in mineral oil). The resulting mixture was stirred until gas generation ended, 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzenesulfonyl-oxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (151 mg, 0.25 mmol) and 18-crown-6 ether (31 mg, 0.12 mmol) were added. The solution was flushed with nitrogen gas before being stirred at 80°C for 25 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (5:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 39 mg (23 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 4.80 (d, J = 16, 1H), 4.67 (d, J = 14, 1H), 4.14-3.99 (m, 2H), 3.84(d, J = 9, 1H), 2.99 (d, J = 17, 1H), 2.70 (dd, J = 17, 5, 1H), 1.60 (s, 9H), 1.56 (s, 9H).

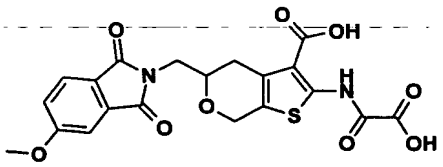
HPLC (254.4 nm) R_t=5.80 min, 95%.

In a 25 ml round bottom flask, 2-(*tert*-butoxyoxalyl-amino)-5-(4,5,6,7-tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (39 mg, 0.06 mmol) was dissolved in 20 % trifluoroaceetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. A precipitate was filtered off and washed with diethyl ether, affording after drying 29 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 4.76 (d, J = 16, 1H), 4.59 (d, J = 14, 1H), 4.0-3.6 (m partially obscured by water, 3H), 3.1 (d partially obscured by water, J = 17, 1H), 2.61 (dd partially obscured by DMSO, J = 20, 11, 1H).

HPLC (254.4 nm) R_t=4.15 min, 75%.

EXAMPLE 3



5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxyphthalic acid (0.25 g, 1.37 mmol) in anhydrous N,N-dimethylformamide (3 ml) under nitrogen was added sodium hydride (0.22 g, 5.48 mmol). The solution was stirred for 5 minutes and then methyl iodide (0.68 ml) was added and continued stirring for 3 h. Several drops of water were added to quench the reaction and the mixture was concentrated in vacuo. The crude material was partitioned between ethyl acetate (40 ml) and water (10 ml). The layers were separated and the organic layer washed with brine (2 x 10 ml), dried(Na_2SO_4), filtered and the solvent evaporated in vacuo. The resulting oil was dissolved in

methanol (8 ml) and 1N sodium hydroxide (4 ml) was added. The reaction was stirred at ambient temperature for 24 h., after which LC-MS indicated only partial hydrolysis. The material was reconstituted in methanol (5 ml) and treated with of sodium hydroxide (0.12 g, 3.0 mmol) dissolved in water (1 ml). The reaction mixture was stirred for 48 h., at which time a precipitate had formed. The mixture was acidified with 6N hydrochloric acid until pH = 1, causing the solution to become homogeneous. The reaction was concentrated in vacuo and the residue partitioned between ethyl acetate (30 ml) and 0.5N hydrochloric acid (10 ml). The layers were separated and the organic layer concentrated in vacuo to give 100 mg (51 %) of 4-methoxy-phthalic acid as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (d, J = 8, 1H), 7.10-7.06 (m, 2H), 3.87 (s, 3H).

LC-MS: R_t=1.45 min, $[M+H]^+$ = 197.1

A solution of 4-methoxy-phthalic acid (0.10 g, 0.51 mmol), 1-hydroxy-benzotriazole (0.15 g, 1.1 mmol), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.22 g, 1.1 mmol), and triethylamine (0.35 ml, 2.5 mmol) was prepared in distilled acetonitrile (4 ml) under nitrogen. 2-Amino-5-aminomethyl-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.11 g, 0.39 mmol) was added in small portions and the reaction was stirred at ambient temperature for 18 h., and then concentrated in vacuo. The crude mixture was diluted in ethyl acetate (30 ml) and washed with 1% hydrochloric acid (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 10 % mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 54 mg (31 %) of 2-amino-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8, 1H), 7.32 (s, 1H), 7.14 (d, *J* = 8, 1H), 4.62-4.48 (m, 2H), 4.00-3.72 (m, 3H), 3.91 (s, 3H), 2.86 (d, *J* = 17, 1H), 2.55 (dd, *J* = 17 , 10, 1H), 1.49 (s, 9H).

To a solution of the above 2-amino-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (54 mg, 0.12 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.25 g, 0.36 mmol) and triethylamine (50 µl, 0.36 mmol). The reaction was stirred for 4 h., concentrated in vacuo and the residue reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic phase was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5% mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 56 mg (81%) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.75 (d, *J* = 8, 1H), 7.32 (d, *J* = 2 , 1H), 7.15 (dd, *J* = 8, 2, 1H), 4.78 (d, *J* = 15, 1H), 4.65 (d, *J* = 15, 1H), 4.03-3.75 (m, 3H), 3.91 (s, 3H), 2.95 (d, *J* = 17, 1H), 2.66 (dd, *J* = 17, 9 , 1H), 1.58 (s, 9H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 574

The above 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno-[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (55 mg, 0.096 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting

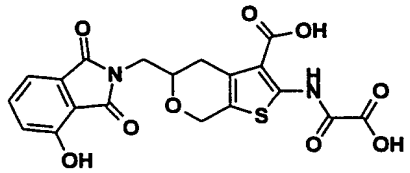
precipitate was washed with dichloromethane and dried in vacuo to give 17 mg (40%) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 7.81 (d, *J* = 8 , 1H), 7.40 (d, *J* = 2, 1H), 7.31 (dd, *J* = 8 , 2, 1H), 4.75 (d, *J* = 15, 1H), 4.56 (d, *J* = 15, 1H), 3.92 (s, 3H), 3.91-3.69 (m, 3H), 2.98 (d, *J* = 17, 1H), 2.57 (dd, *J* = 17, 9, 1H).

APCI-MS: $[M-H]^-$ = 459

HPLC (254.4nm): R_t=3.36 min, 98%

EXAMPLE 4



5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was prepared in a similar way as described in Example 1.

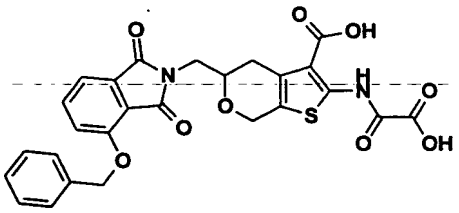
To a solution of the above benzylether (0.7 g, 1.08 mmol) in ethyl acetate (50 ml) was added 10 % palladium on carbon (0.2 g). The mixture was hydrogenated at 1 atm. for 5 h, filtered and the volatiles evaporated in vacuo. The residue (0.6 g) was purified by column chromatography (500 ml silicagel) using a mixture of ethyl acetate/heptane (1:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.4 g (67 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

TLC: R_f = 0.2 (ethyl acetate/heptane 1:1)

The above di-*tert*-butyl ester (0.4 g, 0.72 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (5 ml). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 230 mg (72 %) of the title compound as a solid.

M.p.: > 250 °C;
Calculated for $C_{19}H_{14}N_2O_9S$, 0.5 x H_2O;
C, 50.11 %; H, 3.32 %; N, 6.15 %. Found:
C, 50.06 %; H, 3.17 %; N, 5.98 %.

EXAMPLE 5



5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.7 g, 1.08 mmol) (prepared in a similar way as described in Example 1) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (25 ml). The precipitate was filtered off, washed with diethyl ether and dried in vacuo at 50 °C for 3 h which afforded 400 mg (69 %) of the title compound as a solid..

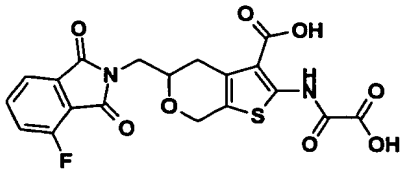
M.p.: 194 - 196 °C;

Calculated for $C_{26}H_{20}N_2O_9S$, 1 x H_2O, 0.6 x CF_3COOH;

C, 52.44 %; H, 3.66 %; N, 4.50 %. Found:

C, 52.33 %; H, 3.65 %; N, 4.62 %.

EXAMPLE 6



5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Prepared in a similar way as described in Example 1.

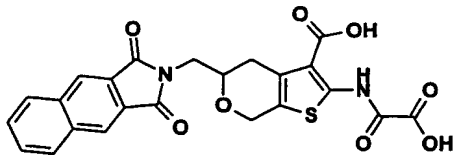
M.p.: > 250 °C;

Calculated for $C_{19}H_{13}FN_2O_8S$, 1 x H_2O;

C, 48.93 %; H, 3.24 %; N, 6.01 %. Found:

C, 48.90 %; H, 3.15 %; N, 5.86 %.

EXAMPLE 7



5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4 ml scintillating vial, a solution of benzo[*f*]isoindole-1,3-dione (145 mg, 0.74 mmol) in N,N-dimethylformamide (2.0 ml) was treated with

potassium hydride (55 mg, 0.48 mmol, 35 % w/w dispersion in mineral oil). The resulting mixture was stirred until gas generation ended and the resulting precipitate was filtered off and washed with dichloromethane which afforded 121 mg (69 %) of benzo[*f*]isoindole-1,3-dione potassium salt as a solid.

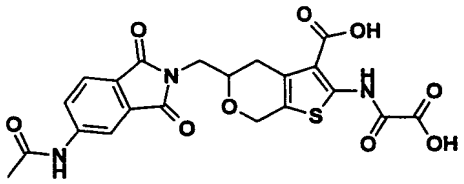
^{1}H NMR (300 MHz, D_2O) δ 8.00-7.87 (m, 4H), 7.62 (s, 2H).

In a 4 ml scintillating vial, the above potassium salt (121 mg, 0.5 mmol) in N,N-dimethylformamide (1.5 ml) was treated with 18-crown-6 ether (34 mg, 0.13 mmol) and 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (148 mg, 0.25 mmol). The solution was flushed with nitrogen gas before being stirred at 80 °C for 7 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of ethyl acetate/dichloromethane (1:49) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 85 mg (57 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-benzo[*f*]isoindole-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.52 (s, 1H), 8.37 (s, 2H), 8.08 (m, 2H), 7.72 (m, 2H), 4.84-4.65 (m, 2H), 4.16-3.90 (m, 3H), 3.02 (d, *J* = 17, 1H), 2.73 (dd, *J* = 17, 10, 1H), 1.61 (s, 9H), 1.58 (s, 9H).

In a 25 ml round bottom flask the above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-benzo[*f*]isoindole-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (85 mg, 0.14 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. The precipitate was filtered off and washed with diethyl ether, affording after drying 62 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.02 (s, 2), 4.81-4.59 (m, 2H), 3.97-3.81 (m partially obscured by water, 3H), 3.08 (d, *J* = 18, 1H), 2.74-2.53 (m partially obscured by DMSO, 1H).

EXAMPLE 8



5-(5-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of N-(1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-acetamide (51 mg, 0.25 mmol) in N,N-dimethylformamide (1.5 ml) under nitrogen at room temperature was added potassium hydride (35 wt.% dispension in mineral oil, 29 mg, 0.25 mmol). The solution was stirred at room temperature for 3 h. A solid precipitated during this period. 2-(*tert*-Butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (100 mg, 0.17 mmol) was added to the suspension and the solution was stirred at 80 °C for 12 h. The solvent was evaporated in vacuo, the resulting residue purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25%) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 50 mg (50 %) of 5-(5-acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

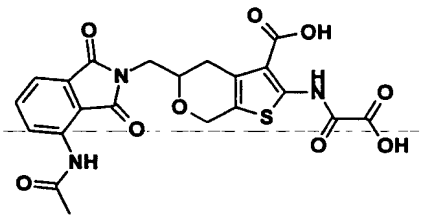
^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 8.03 (d, 1H, *J* = 1.5 Hz), 7.91 (dd, 1H, *J* = 7.8, 1.8 Hz) 7.83 (d, 1H, *J* = 8.1 Hz), 7.45 (s, 1H), 4.80 (d, 1H, *J* = 16 Hz), 4.66 (d, 1H, *J* = 16 Hz), 4.03 (m, 2H), 3.83 (q, 1H, *J* = 15 Hz), 2.98 (d, 1H, *J* = 9 Hz), 2.64-2.78 (m, 1H), 2.27 (s, 3H), 1.62 (s, 9H), 1.57 (s, 9H).

To a mixture of trifluoroacetic acid/dichloromethane (2 ml, 1:1) at room temperature was added the above 5-(5-acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (40 mg, 0.067 mmol). The solution was stirred for 5 h. at which time the solvent was removed in vacuo. The residue was washed with dichloromethane, filtered off, and dried in vacuo which afforded 23 mg (70 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 10.58 (s, 1H), 8.21 (s, 1H) 7.84 (s, 2H), 4.76 (d, 1H, *J* = 15 Hz), 4.58 (d, 1H, *J* = 15 Hz), 3.80-4.00 (m, 3H), 3.00 (d, 1H, *J* = 17 Hz), 2.58-2.73 (m, 1H), 2.13 (s, 3H).

MS: 488 (M+1).

EXAMPLE 9



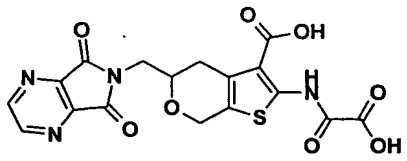
5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described for Example 8.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 9.76 (s, 1H), 8.45 (d, 1H, *J* = 8.4 Hz) 7.79 (t, 1H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 8.4 Hz), 4.77 (d, 1H, *J* = 15 Hz), 4.58 (d, 1H, *J* = 15 Hz), 3.68-3.94 (m, 3H), 3.02 (d, 1H, *J* = 16 Hz), 2.55-2.78 (m, 1H), 2.20 (s, 3H).

MS: 488 (M+1).

EXAMPLE 10



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4-ml scintillating vial, a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (148 mg, 0.5 mmol) in tetrahydrofuran (1.0 ml) was treated with a solution of pyrazine phthtalic acid anhydride (85 mg, 0.56 mmol) in tetrahydrofuran (1.0 ml) and N,N-dimethylformamide (0.5 ml). The reaction mixture was allowed to stir at room temperature for 1 h. Diisopropylethylamine (220 µl, 0.13 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (121 mg, 0.6 mmol) were then added. The reaction mixture was shaken vigorously for 10 seconds before being stirred at room temperature for 14 h. The volatiles were evaporated in vacuo and the residue purified by silica gel chromatography using a mixture of dichloromethane/ethyl acetate (3:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 25 mg (12 %) of the 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) d 8.97 (s, 2H), 4.62-4.49 (m, 2H), 4.21-4.04 (m, 2H), 3.94 (dd, *J* = 14, 4, 1H), 2.91 (d, *J* = 17, 1H), 2.63 (dd, *J* = 17, 10, 1H), 1.68 (s, 9H).

In a 4 ml scintillating vial a solution of the above 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (25 mg, 0.06 mmol) in tetrahydrofuran (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.36 mmol). After stirring for 3 h. at room temperature the

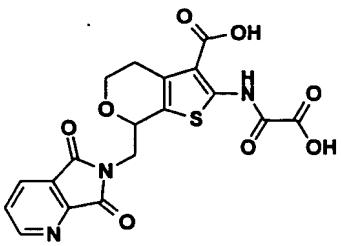
reaction solution was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 31 mg (95 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.96 (s, 2H), 4.80-4.61 (m, 2H), 4.21-4.04 (m, 2H), 3.96 (dd, *J* = 14, 4, 1H), 3.03 (d, *J* = 16, 1H), 2.70 (dd, *J* = 17, 10, 1H), 1.60 (s, 9H), 1.59 (s, 9H).

In a 25 ml round bottom flask the above 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester, (31 mg, 0.06 mmol) was dissolved in 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring for 24 h. A precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid.
^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 9.02 (s, 2), 4.81-4.59 (m, 2H), 3.97-3.81 (m partially obscured by water, 3H), 3.08 (d, *J* = 18, 1H), 2.74-2.53 (m partially obscured by DMSO, 1H).

HPLC (254.4 nm) R_t=2.97 min, 89%.
MS ($APCI^-$) [M-H] 432.4

EXAMPLE 11



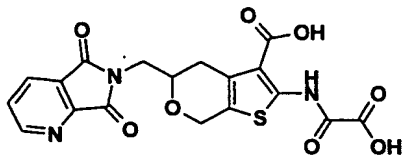
7-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

A solution of furo[3,4-b]pyridine-5,7-dione (86.1 mg, 0.58 mmol) and of 2-(*tert*-butoxyoxalyl-amino)-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (194 mg, 0.47 mmol) in acetonitrile (2.0 ml) was stirred for 10 min. at room temperature. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (89.2 mg, 0.564 mmol) and triethylamine (198 µl, 1.41 mmol) were added and the mixture was stirred at room temperature for 20 h. The volatiles were removed in vacuo and the crude product dissolved in dichloromethane (60 ml) and washed with water (3 x 30ml). The organic layer was dried ($MgSO_4$), filtered and the solvent removal in vacuo. The residue (338 mg) was purified by column chromatography on silica gel utilizing a mixture of hexane/ethyl acetate (90/10 to 50/50) as gradient which afforded after evaporation of the solvent in vacuo 85 mg (33 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihyd-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H NMR (300 MHz, $CDCl_3$), δ 9.00 (d, J = 4.8, 1H), 8.21 (d, J = 7.5, 1H), 7.64 (dd, J = 4.8, J = 6.8, 1H), 5.12 (d, J = 7.2, 1H),4.24-4.1 (m, 2H), 3.97-3.91 (m, 1H), 3.75 (m, 1H), 2.90 (m, 1H), 1.29 (s, 9H), 1.27 (s, 9H).
MS: 544 (M+1).

The above 2-(*tert*-butoxyoxalyl-amino)-7-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihyd-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (47.4 mg, 0.087 mmol) was stirred in 50% trifluoroacetic acid in dichloromethane (2 ml) at room temperature for 5 h. The solvent was removed in vacuo and the residue was washed with diethyl ether (4 x 3.0 ml) and dried which afforded 26.5 mg (70 %) of the title compound as a solid.

^{1}H NMR (400MHz, CD_3OD): δ 8.96 (d, *J* = 5, 1H), 8.30 (d, *J* = 7.6, 1H), 7.79 (dd, *J* = 5.2, *J* = 5.2, 1H), 5.10 (d, *J* = 6.4, 1H), 4.16 (m, 2H), 3.96 (dd, *J* = 3.2, *J* = 3.6, 1H), 3.78 (m, 1H), 2.95 (m, 2H).
MS: 432 (M+1).

EXAMPLE 12



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

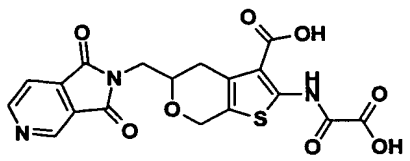
Pyrrolo[3,4-b]pyridine-5,7-dione (74.2 mg, 0.5 mmol) was stirred with sodium hydride (60 % dispersion in mineral oil, 20.04 mg, 0.5 mmol) in N,N-dimethylformamide (4.0 ml) at room temperature under inert atmosphere. 2-(*tert*-Butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (198 mg, 0.33 mmol) was added to the sodium salt formed and the reaction was stirred at 80 °C for 20 h. The solvent was removed in vacuo and the crude product was purified by preparative TLC (hexane:ethyl acetate 50:50) which afforded 58 mg (21 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (d, *J* = 5, 1H), 8.20 (d, *J* = 7.5, 1H), 7.65 (dd, *J* = 5, *J* = 5, 1H), 4.80 (d, *J* = 14.7, 1H), 4.66 (d, J = 14.7, 1H), 4.10 (m, 2H), 3.91 (d, *J* = 13.2, 1H), 3.02 (d, *J* = 16.5, 1H), 2.70 (m, 1H), 1.61 (s, 9H), 1.58 (s, 9H).
MS: 544 (M+1).

The above 2-(*tert*-butoxyoxalyl-amino)-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (46.4 mg, 0.09 mmol) was stirred in 20 % trifluoroacetic acid in dichloromethane (3.0 ml) at room temperature for 2 h. The volatiles were removed in vacuo and the residue was washed with diethyl ether (5 x 3 ml) affording 37 mg (99 %) of the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.96 (d, *J* = 5.4, 1H), 8.20 (d, *J* = 7.7, 1H), 7.64 (m, 1H), 4.77 (d, *J* = 14.7, 1H), 4.61 (d, *J* = 14.7, 1H), 4.07 (m, 2H), 3.86 (d, *J* = 10.5, 1H), 3.12 (d, *J* = 17.4, 1H), 2.77-2.68 (m, 2H).

MS: 432 (M+1).

EXAMPLE 13



5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of pyrrolo[3,4-c]pyridine-1,3-dione (74 mg, 0.50 mmol) in N,N-dimethylformamide (1 ml) under nitrogen at room temperature was added potassium hydride (35 wt.% dispersion in mineral oil, 57 mg, 0.50 mmol). The solution was stirred at room temperature for 3 h. A solid precipitated during this period. 18-Crown-6 (33 mg, 0.13 mmol) and 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-benzene-sulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (150 mg, 0.25 mmol) were then added. The solution was stirred at 80°C for 12 h and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (10-25%) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 93 mg (68 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-

dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

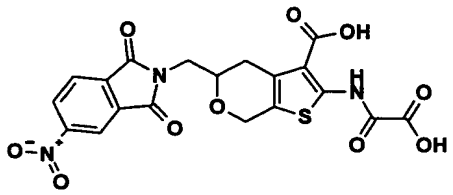
^{1}H NMR ($CDCl_3$): δ 12.49 (s, 1H), 9.20 (s, 1H), 9.11 (d, 2H, *J* = 4.8 Hz) 7.80 (d, 2H, *J* = 4.8 Hz), 4.80 (d, 1H, *J* = 16 Hz), 4.66 (d, 1H, *J* = 16 Hz), 4.00-4.18 (m, 2H), 3.70-3.95 (m, 1H), 3.01 (d, 1H, *J* = 17 Hz), 2.64-2.78 (m, 1H), 1.60 (s, 9H), 1.59 (s, 9H).

To a mixture of trifluoroacetic acid/dichloromethane (1 ml, 1:1) at room temperature was added the above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (29 mg, 0.053 mmol). The solution was stirred for 5 h. and the solvent evaporated in vacuo. The residue was washed with dichloromethane afford after drying in vacuo 22 mg (96 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 9.15 (s, 1H), 9.11 (d, 2H, *J* = 4.8 Hz) 7.92 (d, 2H, *J* = 4.8 Hz), 4.76 (d, 1H, *J* = 15 Hz), 4.58 (d, 1H, *J* = 16 Hz), 3.75-4.00 (m, 4H), 3.04 (d, 1H, *J* = 17 Hz).

MS: 432 (M+1).

EXAMPLE 14



5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 4-ml scintillating vial, a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (58 mg, 0.2 mmol) in tetrahydrofuran (2.0 ml) was treated with 4-nitrophthalic acid (63 mg, 0.3 mmol), diisopropylethylamine (190 μl, 1.1 mmol), and 1,3-

diisopropylcarbodiimide (120 μl, 0.77 mmol). The reaction mixture was shaken vigorously for 10 seconds before being stirred at 50 °C for 43 h. and at room temperature for 20 h. The solution was diluted with ethyl acetate (25 ml), washed with 0.5N aqueous hydrochloric acid (25 ml), saturated aqueous sodium bicarbonate (25 ml), and brine (25 ml). The organic layer was dried($MgSO_4$), filtered and the solvent evaporated in vacuo. Crude 2-amino-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained as a solid and used immediately in the next step.

In a 4 ml scintillating vial a solution of the above crude 2-amino-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester in dichloromethane (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (147 mg, 0.75 mmol). After stirring for 2 h. at room temperature the reaction mixture was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo which afforded 30 mg (26 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.71 (s, 1H), 8.64 (d, *J* = 8, 1H), 8.08 (d, *J* = 9, 1H), 4.79 (d, *J* = 14, 1H), 4.65 (d, *J* = 14, 1H), 4.21-3.97 (m, 2H), 3.89 (d, *J* = 12, 1H), 3.01 (d, *J* = 16, 1H), 2.83-2.61 (m, 1H), 1.63 (ds, 18H).

In a 25 ml round bottom flask, the above 2-(*tert*-butoxyoxalyl-amino)-5-(5-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (30 mg, 0.05 mmol) was dissolved in a mixture of 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring of 24 h.

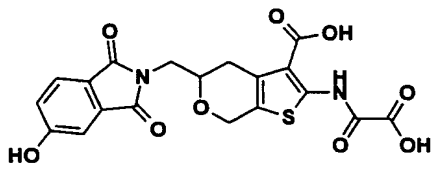
A precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.63 (d, J = 8, 1H), 8.15 (d, J = 8, 1H), 4.76 (d, J = 16, 1H), 4.57(d, J = 16, 1H), 4.42-3.74 (m partially obscured by water, 3H), 3.04 (d partially obscured by water, J = 16, 1H), 2.61 (m partially obscured by DMSO, 1H).

HPLC (254.4 nm) R_t=3.40 min, 86%.

MS (APCI$^+$) [M+H] 407.6

EXAMPLE 15



5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxyphthalic acid (0.45 g, 2.47 mmol) in anhydrous N,N-dimethylformamide (5 ml) under nitrogen was added chloromethyl methyl ether (1.13 ml, 14.8 mmol) and diisopropylethylamine (2.6 ml, 14.8 mmol). The reaction was stirred at ambient temperature for 18 h. and then concentrated in vacuo. The crude material was partitioned between ethyl acetate (50 ml) and water (15 ml). The layers were separated, the organic layer washed with water (3 x 10 ml), brine (2 x 10 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The resulting oil was dissolved in ethanol (5 ml) and sodium hydroxide (0.12 g, 7.4 mmol) dissolved in water (1 ml) was added to the reaction. The solution was stirred at ambient temperature for 48 h. and then concentrated in vacuo affording 4-methoxymethoxy-phthalic acid di-sodium salt which was used without purification.

^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (d, *J* = 8, 1H), 7.06 (d, *J* = 3, 1H), 6.89 (dd, *J* = 8, 3, 1H), 5.18 (s, 2H), 3.42 (s, 3H).

A solution of 4-methoxymethoxy-phthalic acid di-sodium salt (0.19 g, 0.70 mmol), 1-hydroxybenzotriazole (0.2 g, 3.6 equiv.), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.28 g, 3.6 equiv.), and triethylamine (0.33 ml, 6 equiv.) was prepared in distilled acetonitrile (5 ml) under nitrogen. The mixture was stirred for 5 minutes before 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (115 mg, 0.40 mmol) was added in small portions. The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo. The crude mixture was diluted with ethyl acetate (30 ml) and washed with 1% hydrochloric acid (5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (5 to 10% gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 44 mg (23 %) of 2-amino-5-(5-methoxy-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8, 1H), 7.48 (d, *J* = 2, 1H), 7.27 (dd, *J* = 8, 2, 1H), 5.26 (s, 2H), 4.60-4.46 (m, 2H), 3.99-3.71 (m, 3H), 3.47 (s, 3H), 2.85 (d, *J* = 17, 1H), 2.55 (dd, *J* = 17, 9, 1H), 1.48 (s, 9H).

To a solution of the above 2-amino-5-(5-methoxy-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (44 mg, 0.095 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (56 mg, 0.29 mmol) and triethylamine (26 μl, 0.19 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and

brine (5 ml). The resulting solution was dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 35 mg (63 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.75 (d, *J* = 8, 1H), 7.49 (d, *J* = 2, 1H), 7.28 (dd, *J* = 8, 2, 1H), 5.26 (s, 2H), 4.77 (d, *J* = 15, 1H), 4.64 (d, *J* = 15, 1H), 4.03-3.74 (m, 3H), 3.47 (s, 3H), 2.95 (d, *J* = 17, 1H), 2.65 (dd, *J* = 17, 9, 1H), 1.58 (s, 9H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 603.7

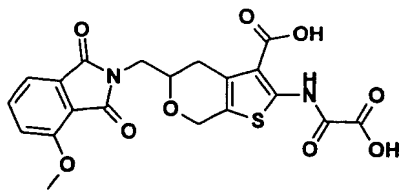
The above 2-(*tert*-butoxyoxalyl-amino)-5-(5-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (35 mg, 0.058 mmol) was dissolved in a mixture of 50 % trifluoroacetic acid/dichloromethane (2.5 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 20 mg (77 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 10.97 (s, 1H), 7.72 (d, *J* = 8, 1H), 7.18 (s, 1H), 7.10 (d, *J* = 8, 1H), 4.74 (d, *J* = 15, 1H), 4.58 (d, *J* = 15, 1H), 3.96-3.62 (m, 3H), 2.99 (d, *J* = 17, 1H), 2.60-2.50 (m, 1H, partially obscured by DMSO).

APCI-MS: $[M-H]^-$ = 445.4

HPLC (254.4nm): R_t=2.92 min, 95%

EXAMPLE 16



5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (195 mg, 1.2 mmol) in anhydrous N,N-dimethylformamide (4 ml) under nitrogen was added sodium hydride (61 mg, 1.56 mmol). The solution was stirred for 15 minutes and then methyl iodide (0.37 ml, 6.0 mmol) was added. The reaction was stirred for 48 h. and then quenched with saturated ammonium chloride. The mixture was concentrated in vacuo, diluted in ethyl acetate (20 ml) and the organic phase washed with 1N hydrochloric acid (5 ml) and brine (3 x 5 ml). The organic layer was dried($MgSO_4$) and concentrated in vacuo. To the crude solid was added methanol causing a precipitate to form. The flask was cooled in an ice bath for 2 h. and the solid filtered off, washed with methanol and dried in vacuo which afforded 0.1 g (47 %) of 4-methoxy-isobenzofuran-1,3-dione as a solid.
^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (t, J = 8, 1H), 7.61 (d, J = 8, 1H), 7.58 (d, J = 8, 1H), 3.99 (s, 3H).
APCI-MS: $[M+H]^+$ = 179.1

A solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (122 mg, 0.43 mmol, prepared as described in Example 17) and 4-methoxy-isobenzofuran-1,3-dione (92 mg, 0.52 mmol) was prepared in distilled tetrahydrofuran (4 ml) under nitrogen. 1-hydroxybenzotriazole (87 mg, 0.65 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (123 mg, 0.65 mmol), and triethylamine (0.29 ml, 2.15 mmol) were added. The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo. The crude mixture was diluted with ethyl acetate (25 ml) and washed with 1N hydrochloric acid (5

ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 0.18 g (94 %) of 2-amino-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7, 1H), 7.43 (d, *J* = 7 , 1H), 7.19 (d, *J* = 7, 1H), 4.59-4.46 (m, 2H), 4.06-3.72 (m, 3H), 4.00 (s, 3H), 2.87-2.81 (m, 1H), 2.60-2.51 (m, 1H), 1.48 (s, 9H).

To a solution of the above 2-amino-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.18 g, 0.42 mmol) in distilled dichloromethane (5 ml) under nitrogen was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.25 g, 1.26 mmol) and triethylamine (0.23 ml, 1.68 mmol). The reaction was stirred for 12 h., concentrated in vacuo and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The resulting solution was dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 10 % gradient). Pure fractions were collected and the solvent evaporated in vacuo to give 195 mg (81 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.48 (s, 1H), 7.65 (t, *J* = 7, 1H), 7.43 (d, *J* = 7, 1H), 7.19 (d, *J* = 7, 1H), 4.77 (d, *J* = 15, 1H), 4.63 (d, *J* = 15, 1H), 4.04-3.75 (m, 3H), 4.00 (s, 3H), 2.94 (d, *J* = 17, 1H), 2.65 (dd, *J* = 17, 10, 1H), 1.58 (s, 9H), 1.53 (s, 9H).

LC-MS: R_t=4.17 min, $[M+H]^+$ = 573.2

The above 2-(*tert*-butoxyoxalyl-amino)-5-(4-methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-

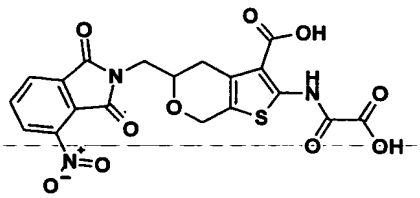
carboxylic acid *tert*-butyl ester (0.15 g, 0.26 mmol) was dissolved in a mixture of 50 % trifluoroacetic acid/dichloromethane (5 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 100 mg (83 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 7.79 (t, *J* = 8, 1H), 7.48 (d, *J* = 8, 1H), 7.42 (d, *J* = 8, 1H), 4.74 (d, *J* = 15, 1H), 4.56 (d, *J* = 15, 1H), 3.95 (s, 3H), 3.91-3.79 (m, 2H), 3.69-3.63 (m, 1H), 2.98 (d, *J* = 17, 1H), 2.57 (dd, *J* = 17, 10, 1H).

LC-MS: R_t=1.26 min, $[M+H]^+$ = 461.0

HPLC (254.4nm): R_t=3.10 min, 100%

EXAMPLE 17



5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

In a 50-ml round-bottom flask, a suspension of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (2.00 g, 4.8 mmol) in absolute ethanol (20 ml) was flushed with nitrogen and sealed with a rubber septum. Hydrazine (0.5 ml, 15.9 mmol) was added, followed by an additional portion of absolute ethanol (20 ml) at room temperature. The reaction mixture was heated to 80 °C for 3.5 h., then allowed to stir at room temperature for 14 h. The precipitate was filtered off and washed with absolute ethanol. The filtrate was concentrated in vacuo leaving an oil, which was dissolved in dichloromethane (30 ml) and refiltered. The solvent was evaporated in

vacuo affording 1.2 g (86 %) of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) d 5.92 (s, 2H), 4.64 (s, 2H), 3.68-3.60 (m, 1H), 2.98-2.74 (m, 3H), 2.56-2.44 (m, 1H), 1.54 (s, 9H).
MS ($APCI^+$) [M+H] 285.3

In a 4-ml scintillating vial, a solution of the above 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (63 mg, 0.2 mmol) in tetrahydrofuran (2.0 ml) was treated with 3-nitro-phthalic acid (66 mg, 0.3 mmol), diisopropylethylamine (190 µl, 1.1 mmol), and 1,3-diisopropyl-carbodiimide (120 µl, 0.77 mmol). The reaction mixture was shaken vigorously for 10 seconds before being stirred at 50°C for 43 h. and at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate (25 ml) and washed with 0.5N aqueous hydrochloric acid (25 ml), saturated sodium bicarbonate (25 ml), and brine (25 ml). The organic layer was dried($MgSO_4$), filtered and the solvent evaporated in vacuo affording crude 2-amino-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

In a 4 ml scintillating vial a solution of the above crude 2-amino-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester in dichloromethane (3 ml) was treated with midazol-1-yl-oxo-acetic acid *tert*-butyl ester (147 mg, 0.75 mmol). After stirring for 2 h. at room temperature the reaction solution was concentrated to dryness in vacuo. The residue was purified by silica gel chromatography using a mixture of hexanes/ethyl acetate (3:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 30 mg (26%) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

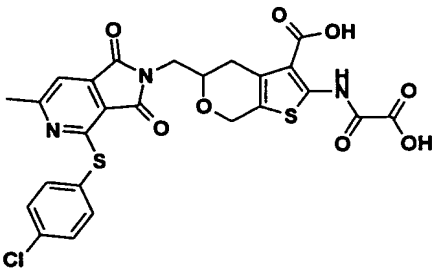
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5, 1H), 8.11 (d, *J* = 6, 1H), 7.94 (t, *J* = 8, 1H), 4.80 (d, *J* = 14, 1H), 4.67 (d, *J* = 15, 1H), 4.16-3.97 (m, 3H), 3.88 (d, *J* = 10, 1H), 3.01 (d, *J* = 16, 1H), 2.70 (dd, *J* = 16, 10, 1H), 1.62 (s, 9H), 1.59 (s, 9H).

In a 25 ml round bottom flask, the above 2-(*tert*-butoxyoxalyl-amino)-5-(4-nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (30 mg, 0.05 mmol) was dissolved in a mixture of 20 % trifluoroacetic acid in dichloromethane (4 ml). The solution was left open to the atmosphere without stirring. After standing for 24 h. a precipitate was filtered off and washed with diethyl ether, affording after drying 22 mg (90 %) of the title compound as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.32 (d, *J* = 9, 1H), 8.20 (d, *J* = 9, 1H), 8.07 (t, *J* = 9, 1H), 4.77 (d, *J* = 14, 1H), 4.59 (d, *J* = 16, 1H), 4.00-3.65 (m partially obscured by water, 3H), 3.04 (d partially obscured by water, *J* = 16, 1H), 2.63 (dd partially obscured by DMSO, *J* = 17, 13, 1H).

~~HPLC (254.4 nm) R_t= 3.33 min, 100%.~~

MS (APCI$^+$) [M+H] 391.6

EXAMPLE 18



5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Under a nitrogen atmosphere, 4-(4-chloro-phenylsulfanyl)-6-methyl-pyrrolo[3,4-c]-1,3-dione (914 mg, 3.0 mmol), tributylphosphine (1.66 ml, 4.5 mmol) and 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (855 mg, 3.0 mmol) were successively dissolved in dry benzene (90 ml). Solid azodicarboxylic dipiperidine (1.13 g, 4.5 mmol) was added under stirring at 0 °C to the solution. After stirring for 10 min, the reaction mixture was brought to room temperature and the stirring continued for 4 h. The mixture was cooled on ice, and additional portions of tributylphosphine (1.66 ml, 4.5 mmol) and azodicarboxylic dipiperidine (1.13 g, 4.5 mmol) were added. After stirring for 10 min, the reaction mixture was brought to room temperature and the stirring continued for 18 h. Heptane (30 ml) was added to the reaction and the precipitate filtered off (discard). After evaporation of the solvent the product was purified by flash chromatography to give 1.3 g (76 %) of 2-amino-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

Mp: 118 - 119° C;

^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.50 (s, 3H), 2.50-2.65 (m, 1H), 2.85- 2.95 (m, 1H), 3.75-3.85 (m, 1H), 3.95- 4.05, (m, 2H), 4.50- 4.15 (m, 2H), 5.95 (bs, 2H), 7.30 (s, 1H), 7.40 (d, 2H), 7.55 (d, 2H).

To a ice cooled solution of 2-amino-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (572 mg, 1 mmol) and dry triethylamine (2 ml) in dry tetrahydrofuran (10 ml) was added imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (588 mg, 3 mmol). After 10 min, the reaction mixture was brought to room temperature and the stirring continued for 18 h. The mixture was concentrated in vacuo and submitted to flash chromatography using a mixture of toluene/ethyl acetate (30:1) as eluent. Pure fraction were collected and the solvent evaporated in vacuo

to give 360 mg (51 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

M.p.: 134 - 136° C;

^{1}H NMR ($CDCl_3$) δ 1.60 (s, 9H), 1.63 (s, 9H), 2.50 (s, 3H), 2.65-2.75 (m, 1H), 2.95- 3.05 (m, 1H), 3.75-3.90 (m, 1H), 4.00- 4.10, (m, 2H), 4.60- 4.85 (m, 2H), 7.30 (s, 1H), 7.40 (d, 2H), 7.55 (d, 2H), 12.50 (s, 1H).

To 2-(*tert*-butoxyoxalyl-amino)-5-(4-(4-chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (324 g, 0.46 mmol) was added a mixture of trifluoroacetic acid (2.5 ml) and dichloromethane (7.5 ml). The mixture was stirred for 5 h, and added petroleum ether/ethyl acetate. The precipitate was isolated off and re-suspended in ethyl acetate. The title compound 136 mg (50 %) was isolated by filtration.

Mp: 239 - 240° C;

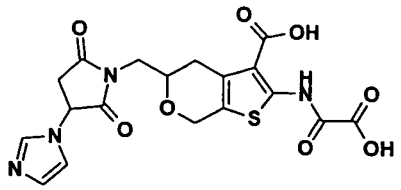
Calculated for $C_{25}H_{18}ClN_3O_8S_2$, 0.75 x H_2O;

C, 49.92 %; H, 3.27 %; N, 6.99 %. Found:

C, 49.83 %; H, 3.16 %; N, 6.85 %.

^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.65-2.75 (m, 1H), 2.95- 3.05 (m, 1H), 3.50-4.00 (m, 3H), 4.50- 4.90 (m, 2H), 7.50-7.68 (m, 5H), 12.30 (s, 1H).

EXAMPLE 19



5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.53 g, 1.86 mmol, prepared as described in Example 17) in tetrahydrofuran (10 ml) was added, maleic acid (0.24 g, 2.05 mmol) and diisopropylcarbodiimide (0.58 ml, 3.72 mmol). The reaction mixture was heated to reflux for 3 h. and then allowed to cool to room temperature over an 18 h. period. The solvent was stripped off in vacuo and the residue diluted into ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (2 x 50 ml), 1 % hydrochloric acid (2 x 20 ml), brine (3 x 50 ml), dried($MgSO_4$), filtered, and the solvent evaporated in vacuo affording an oil which was subjected to flash chromatography using a mixture of ethyl acetate/hexanes (6:4) as eluent. Pure fractions (R_f=0.25) were collected and the solvent evaporated in vacuo to give 0.60 g (90 %) of 2-amino-5-(2,5-dioxo-2,5-dihydro-pyrrol-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 5.7, 1H), 6.63 (d, *J* = 5.4, 1H), 5.94 (bs, 2H), 4.67 (s, 2H), 3.93 (m, 1H), 3.82 (m, 2H), 2.89-2.83 (m, 1H), 2.69-2.60 (m, 1H), 1.54 (s, 9H).

MS: APCI (+): 365.2 (M+H);

To a solution of the above 2-amino-5-(2,5-dioxo-2,5-dihydro-pyrrol-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (60 mg, 1.64 mmol) in tetrahydrofuran (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (50 mg, 2.46 mmol). The

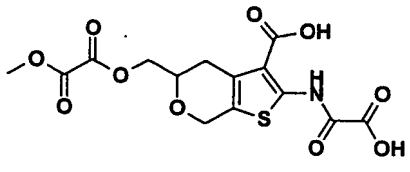
solution was stirred at room temperature for 48 h. The solvent was stripped off in vacuo and the resultant oil diluted in ethyl acetate (20 ml), washed with brine (3 x 25 ml), dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9) as eluent which afforded 25 mg (28 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(3-imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a mixture of diastereoisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.94 (s, 1H), 5.92 (m, 1H), 5.22 (m, 1H), 4.68-4.53 (m, 2H), 4.00 (m, 3H), 3.71 (m, 1H), 3.47-3.38 (m, 1H), 3.03-2.87 (m, 1H), 2.61 (m, 1H), 1.60 (s, 9H), 1.54 (s, 9H).
MS: APCI (+): 561.2 (M+H).

To the above 2-(*tert*-butoxyoxalyl-amino)-5-(3-imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (25 mg, 0.05 mmol) was added a mixture of 20% trifluoroacetic acid in dichloromethane (2 ml). The reaction mixture was allowed to stir at room temperature for 2 h., at which time the mixture was concentrated in vacuo. The resultant solid was triturated with diethyl ether (2x) which afforded 13 mg (65 %) of the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 9.15 (s, 1H), 7.78 (s, 1H), 7.63 (m, 1H), 5.75 (m, 1H), 4.69 (m, 2H), 4.46 (m, 1H), 3.85 (m, 2H), 3.66 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 2.64 (m, 1H), 2.46 (m, 1H).
MS: ESI (-): 447.4 (M-H).

EXAMPLE 20



Oxalic acid 3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl

To a solution of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (8.0 g, 28 mmol) in dry tetrahydrofuran (50 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (27.51 g, 0.14 mol) and triethylamine (3.93 ml, 0.14 mol). The reaction mixture was stirred at room temperature for 20 h. The volatiles were removed in vacuo and the crude product was dissolved in ethyl acetate (300 ml) and washed with a saturated solution of sodium bicarbonate (3 x 100 ml), dilute hydrochloric acid (3 x 100 ml), water (3 x 100 ml) and brine (100 ml). The organic layer was dried($MgSO_4$), filtered and the solvent removed in vacuo affording a foam (16 g) which was purified on column chromatography on silica gel using a gradient of hexane/ethyl acetate (90:10 to 50:50 gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo which afforded 11 g (91 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester *tert*-butyl ester as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 2H), 4.86 (d, J = 14.7, 1H), 4.77 (d, J = 14.4, 1H), 4.64 (m, 1H), 3.82-3.71 (m, 2H), 2.85 (d, J = 16.8, 1H), 2.68 (d, J = 10.5, 1H), 1.62 (s, 9H), 1.61 (s, 9H).

MS: 414 (M+1).

A solution of the above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester *tert*-butyl ester (8.3 g, 20.1 mmol) and potassium carbonate (1.7 g, 12.3 mmol) was stirred in methanol (80 ml) in presence of water (3 ml) at room temperature for 10 min., at which time TLC indicated reaction complete. Methanol was removed in vacuo and the crude product was dissolved in dichloromethane (300 ml) and washed with water (3 x 150 ml). The organic phase was dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified on flash chromatography on silica gel using a gradient of hexane/ethyl acetate (90:10 to 50:50 gradient) as

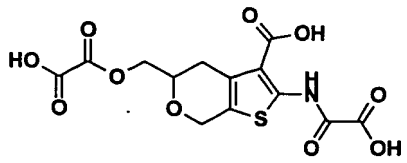
eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.65 g (9 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.86 (d, *J* = 15, 1H), 4.78 (d, *J* = 15, 1H), 4.00 (s, 3H), 3.82-3.70 (m, 3H), 2.86 (d, *J*= 17, 1H), 2.66 (dd, *J* = 10.2, *J* = 10.5, 1H), 1.62 (s, 9H).
MS: 316 (M-55).

To a solution of the above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester (160 mg, 0.43 mmol) in dry tetrahydrofuran (3.0 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (420.4 mg, 2.15 mmol) and triethylamine (120 µl, 0.86 mmol). The resulting mixture was stirred at room temperature for 20 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel using a gradient of hexane/ethyl acetate (95:5 to 80:20 gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 173 mg (81 %) of oxalic acid 2-amino-3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (dd, *J* = 14.7, *J* = 14.2, 2H), 4.40 (m, 2H), 4.00 (s, 3H), 2.96 (d, *J* = 15.3, 1H), 2.69 (dd, *J* = 10.8, *J* = 10.8, 1H), 1.61 (s, 9H), 1.57 (s, 9H).
MS: 388.3 (M-11).

The above oxalic acid 2-amino-3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl ester methyl ester (93.8 mg, 0.19 mmol) was stirred in 20 % trifluoroacetic acid in dichloromethane (2 ml) for 20 h. at room temperature. The solvent was removal in vacuo which afforded 73 mg (95 %) of the title compound as a solid.
^{1}H NMR (300 MHz, CD_3OD): δ 4.76 (d, *J* = 5.7, 2H), 4.18 (d, *J* = 4.8, 2H), 3.97 (s, 3H), 2.99 (d, *J* = 16.2, 1H), 2.65 (d, *J* = 10.8, 1H).

MS: 386 (M-1).

EXAMPLE 21



Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester

To a solution of a mixture of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1:4 estimated based on ^{1}H NMR) (200 mg, 0.70 mmol) and diisopropylethylamine (0.25 ml, 1.4 mmol) in dichloromethane (6.0 ml) cooled to 0 °C under nitrogen was added triethylchlorosilane (0.18 ml, 1.1 mmol). The solution was stirred at 0 °C for 5 min. and then stirred at room temperature for 15 min. The solution was washed with saturated sodium bicarbonate and brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/hexane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 42 mg (16 %) of 2-amino-5-triethylsilanyloxymethy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**1**) and 193 mg (69 %) of 2-amino-7-triethylsilanyloxy-methy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**2**).

(**1**) ^{1}H NMR ($CDCl_3$): δ 4.58 (m, 1H), 4.18-4.07 (m, 1H), 3.84 (dd, 1H, J = 9.6, 6.0 Hz), 3.80-3.70 (m, 1H), 3.60 (dd, 1H, J = 9.6, 7.8 Hz), 2.92-2.70 (m, 2H), 1.58 (s, 9H), 0.98 (t, 9 H, J = 7.8 Hz), 0.64 (q, 6H, J = 7.8 Hz);

(2) ^{1}H NMR ($CDCl_3$): δ 4.62 (s, 2H), 3.85-3.64 (m, 3H), 2.82 (dm, 1H, *J* = 15 Hz), 2.49 (dd, 1H, *J* = 15, 11 Hz), 1.58 (s, 9H), 0.98 (t, 9 H, *J* = 7.8 Hz), 0.64 (q, 6H, *J* = 7.8 Hz).

To a solution of 2-amino-7-triethylsilanyloxymethy-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (6.0 g, 15 mmol) in dichloromethane (10 ml) cooled to 0 °C under the nitrogen was added a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (4.5 g, 18 mmol) in dichloromethane. The solution was stirred at 0 °C for 10 min. The reaction was quenched with water (1.0 ml). The solution was washed with brine and dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 10% mixture of ethyl acetate/hexane as eluent. Pure fractions of two compounds were collected and the solvent evaporated in vacuo affording 4.5 g (56 %) of 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**A**) as a solid and 50 mg of oxalic acid 3-(*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H- thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**B**) as a solid.

(**A**) ^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 4.85 (d, 1H, *J* = 12 Hz), 4.65 (d, 1H, *J* = 12 Hz), 3.90-3.60 (m, 3H), 2.94 (d, 1H, *J* = 15 Hz), 2.63 (dd, 1H, *J* = 15, 11 Hz), 1.63 (s, 9H), 1.61 (s, 9H), 0.98 (t, 9 H, *J* = 7.8 Hz), 0.64 (q, 6H, *J* = 7.8 Hz).

(**B**) ^{1}H NMR ($CDCl_3$): δ 12.47 (s, 1H), 4.82 (q, 2H, *J* = 14 Hz), 4.43 (m, 2H), 4.01 (m, 1H), 2.97 (d, 1H, *J* = 14 Hz), 2.69 (dd, 1H, *J* = 19, 9 Hz), 1.63 (s, 9H), 1.61 (s, 9 H), 1.58 (s, 9H).

To a solution of the above 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyl-oxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.5 g, 8.5 mmol) in tetrahydrofuran (10 ml) at room

temperature was added 0.5 N hydrochloric acid (2.0 ml). The solution was stirred at room temperature for 0.5 h. Ethyl acetate (100 ml) was added and the resulting solution was washed with saturated sodium bicarbonate, brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a 10 % mixture of ethyl acetate/hexane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 3.0 g (84 %) of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR ($CDCl_3$): δ 12.53 (s, 1H), 4.86 (d, 1H, *J* = 12 Hz), 4.60 (d, 1H, *J* = 12 Hz), 3.85-3.65 (m, 3H), 2.85 (d, 1H, *J* = 15 Hz), 2.65 (dd, 1H, *J* = 15, 11 Hz), 1.63 (s, 9H), 1.61 (s, 9H).

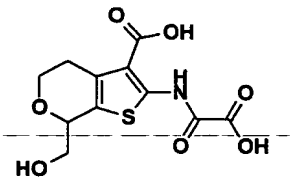
To a solution of the above 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (3.0 g, 7.1 mmol) in dichloromethane (10 ml) at room temperature was added pyridine (2.5 ml, 28.5 mmol) and 4-nitrobenzenesulfonyl chloride (4.7 g, 21.4 mmol). The solution was heated to 50 °C and stirred for 4.5 h. The solution was cooled to room temperature and washed with 0.5 N hydrochloric acid, saturated sodium bicarbonate, brine, dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (0-100 %) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 3.6 g (84 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(4-nitrobenzenesulfonyloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR ($CDCl_3$): δ 12.40 (s, 1H), 8.43 (d, 2H, *J* = 9.0 Hz), 8.17 (d, 2H, *J* = 9.0 Hz), 4.72 (d, 1H, *J* = 14 Hz), 4.64 (d, 1H, *J* = 14 Hz), 4.38-4.24 (m, 2H), 3.98-3.86 (m, 1H), 2.92 (d, 1H, *J* = 17 Hz), 2.65 (dd, 1H, *J* = 17, 12 Hz), 1.63 (s, 9H), 1.61 (s, 9H).
MS: 598 (M-1).

To a solution of 50 % trifluoroacetic acid/dichloromethane (1 ml) at room temperature was added oxalic acid 3-(*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H- thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (50 mg, 0.092 mmol). The solution was stirred for 3 h. The solvent was removed in vacuo. The residue was washed with dichloromethane affording after filtration 25 mg (73 %) of the title compound as a solid.

^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 4.82 (d, 1H, *J* = 15 Hz), 4.68 (d, 1H, *J* = 15 Hz), 4.37 (s, 1H), 3.92 (m, 1H), 2.93 (d, 1H, *J* = 16 Hz), 2.60 (dd, 1H, *J* = 30, 10 Hz).

MS: 372 (M-1).

EXAMPLE 22



7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of 2-hydroxymethyl-tetrahydro-pyran-4-one (35 g, 0.27 mol), *tert*-butyl cyanoacetate (58.68 ml g, 0.4 mol), and sulphur (9.47 g, 0.3 mol) in absolute ethanol (400 ml) was added morpholin (47 ml, 0.54 mol), and the resulting mixture was heated to 45 °C for 16 h. The reaction mixture was cooled, filtered and the filtrate evaporated in vacuo. The resultant oil was dissolved in ethyl acetate (600 ml), washed with water (3 x 200 ml), brine (200 m), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue was crystallised from diethyl ether (100 ml) followed by addition of a mixture of diethyl ether and heptane (100 ml, 1:1). The precipitate was filtered off, washed with a mixture of diethyl ether and heptane (90 ml, 1:1) and dried in vacuo at 50 °C for 52 h affording 44.51 g

of a mixture of 5 and 7 regioisomers according to NMR. The mixture of regioisomers (44.51 g) was suspended in diethyl ether (500 ml) and stirred at room temperature for 96 h. and at reflux temperature for 2 h. After cooling to room temperature the precipitate was filtered off and washed with a mixture of diethyl ether and heptane (100 ml, 1:1) which afforded after drying in vacuo at 50 °C, 22.12 g (29 %) of 2-amino-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

All filtrates were pooled and evaporated in vacuo affording 55 g of a mixture of regioisomers. To 40.16 g (0.141 mol) of this regioisomer mixture dissolved in dichloromethane (450 ml) was added diisopropyl-ethylamine (49.5 ml, 0.28 mol) and the mixture was cooled to 0 °C. Chlorothiethylsilane (38.2 ml, 0.23 mol) was added dropwise and the mixture was stirred for 10 minutes and for 15 minutes at room temperature. The reaction mixture was washed with saturated aqueous sodium carbonate (3 x 150 ml), brine (3 x 150 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (70.4 g) was partitioned into two portions which were subjected to flash chromatography (2 l silicagel) using a mixture of ethyl acetate/hexane (1:20) as eluent. Pure fractions of 2-amino-5-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-7-triethylsilanyl-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester were collected. A fraction containing both isomers (18.84 g) was re-subjected to flash chromatography (2 l silicagel) using a mixture of ethyl acetate/hexane (1:20) as eluent. A total of 28.1 g (50 %) of 2-amino-5-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained. A total of 18.2 g (32 %) of 2-amino-7-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained.

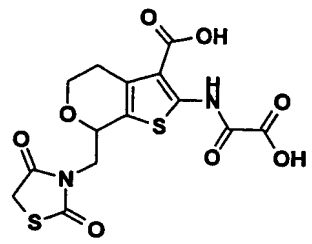
To the above 2-amino-7-triethylsilanylhydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (18.2 g, 0.046 mol)

dissolved in dichloromethane (200 ml) was added a mixture of imidazol-1-yl-oxo-acetic acid *tert* butyl ester (17.9 g, 0.091 mol) in dichloromethane (30 ml) under nitrogen. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction mixture was evaporated in vacuo and the residue was dissolved in ethyl acetate (100 ml) and washed with 1 N hydrochloric acid (3 x 50 ml), brine (3 x 75 ml), dried (Na_2SO_4), filtered and the organic phase evaporated in vacuo affording in quantitative yield 2-(*tert*-butoxyoxalyl-amino)-7-triethylsilanyloxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester ester as a oil.

To a mixture of the above 7-triethylsilanyl ether (24.0 g, 0.046 mol) in tetrahydrofuran (100 ml) was added 1 N hydrochloric acid (18 ml) and the reaction mixture was stirred at room temperature for 1.5 h. Ethyl acetate (150 ml) was added and the reaction mixture was washed with saturated aqueous sodium carbonate (3 x 100 ml), brine (3 x 100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue was trituated with a mixture of diethyl ether and heptane (1:5) and the precipitate was filtered off, washed with heptane and dried in vacuo at 50 °C for 16 h affording 13.55 g (57 %) of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

The above 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (16 mg, 0.033 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (1 ml). The reaction was stirred at room temperature for 3 h. The volatiles were evaporated in vacuo and the residue washed with dichloromethane which afforded 7 mg (73 %) of the title compound as a solid.
^{1}H NMR (DMSO-d_6): δ 12.32 (s, 1H), 4.62 (s, 1H), 4.12 (m, 1H), 3.62-3.78 (m, 2H), 3.40-3.52 (m, 1H), 2.83 (m, 2H).
MS: 300 (M-1).

EXAMPLE 23



7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.13 g, 0.46 mmol) in tetrahydrofuran (3 ml) was added triphenylphosphine (0.13 g, 0.51 mmol), and 2,4-thiazolidinedione (60 mg, 0.51 mmol). The reaction mixture was cooled to 0 °C and diisopropylazodicarboxylate (99 µl, 0.51 mmol) was added via syringe. The resultant mixture was stirred for 18 h., gradually warming to room temperature. The volatiles were evaporated in vacuo and the resulting oil was diluted in ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to flash chromatography using a mixture of dichloromethane/methanol (9:1) as eluent. Pure fractions were collected (R_f=0.70) and the solvent evaporated in vacuo which afforded 89 mg (51 %) of 2-amino-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (s, 2H), 4.82 (dm, 1H), 4.13-4.02 (bm, 2H), 3.99 (s, 2H), 3.75-3.67 (m, 1H), 3.60 (dd, *J* = 14, 3.3, 1H), 2.81-2.74 (m, 2H), 1.54 (s, 9H).

MS: APCI (+): 385.6 (M+H).

To a solution of the above of 2-amino-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (89 mg) in tetrahydrofuran (5 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (79 mg, 0.312 mmol) and the mixture allowed to stir overnight at room temperature. The volatiles were evaporated in vacuo, the residue diluted with ethyl acetate and subjected to preparative chromatography using a mixture of dichloromethane/methanol (9:1) as eluent. Material eluting with R_f= 0.72 was collected and the solvent evaporated in vacuo affording 40 mg (25 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.53 (s, 1H), 5.03 (dm, 1H), 4.12-4.04 (m, 2H), 4.01 (s, 2H), 3.79-3.71 (m, 2H), 2.88 (m, 2H), 1.62 (s, 9H), 1.59 (s, 9H).

MS: APCI (+): 513.3 (M+H).

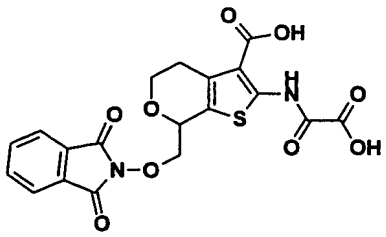
The above 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (40 mg) was dissolved in 50 % trifluoroacetic acid in dichloromethane (1 ml) and stirred at room temperature for 3 h. The mixture was concentrated in vacuo, the residue titurated with dichloromethane and methanol which afforded after drying in vacuo 18 mg (87 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6 + CD_3OD) δ 4.98 (dm, 1H), 4.16 (s, 2H), 4.14-4.02 (m, 2H), 3.78-3.72 (m, 2H), 2.91 (m, 2H).

APCI (-): 399 (M-H);

LC-MS: s, 99%.

EXAMPLE 24



7-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.5 g, 1.2 mmol), 2-hydroxy-isoindole-1,3-dione (0.21 g, 1.3 mmol) and triphenylphosphine (0.35 g, 1.33 mmol) in dry tetrahydrofuran (20 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (205 µl, 1.33 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo and the resultant solid dissolved in ethyl acetate (50 ml). The organic phase was washed with saturated aqueous sodium hydrogencarbonate (3 x 30 ml), water (3 x 50 ml), dried(Na_2SO_4), filtered and evaporated in vacuo. The residue (1.02 g) was subjected to flash column chromatography (300 ml silicagel) using a mixture of ethyl acetate/hexane (1:2) as eluent. Pure fractions were collected affording after evaporation in vacuo 0.37 g (54 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(1,3-dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

The above di-*tert*-butyl ester (0.33 g, 0.59 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (2 ml). The reaction was stirred at room temperature for 6.5 h. The volatiles were evaporated in vacuo and the residue trituated with a mixture of diethyl ether and heptane (5 ml, 1:1). The precipitate was filtered off, washed with heptane and diethyl ether, dried in vacuo at 50 °C for 18 h which afforded 200 mg (77 %) of the title compound as a solid.

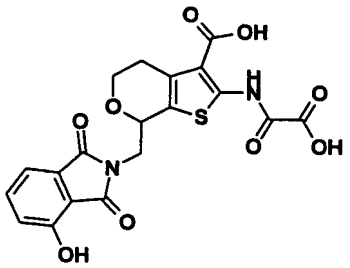
M.p.: 251.5 - 254 °C;

Calculated for $C_{19}H_{14}N_2O_9S$;

C, 51.12 %; H, 3.16 %; N, 6.28 %. Found:

C, 51.46 %; H, 3.71 %; N, 5.87 %.

EXAMPLE 25



7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 4-hydroxy-isobenzofuran-1,3-dione (0.5 g, 3.03 mmol) in anhydrous N,N-dimethylformamide (6 ml) under nitrogen was added diisopropylethylamine (1.05 ml, 6.06 mmol). The solution was stirred with cooling in an ice bath and chloromethyl methyl ether (0.46 ml, 6.06 mmol) was added. The reaction was allowed to slowly warm to ambient temperature and then stirred for an additional 7 h. The mixture was concentrated in vacuo to a small volume and diluted with ethyl acetate (75 ml). The organic layer was washed with water (2 x 40 ml), brine (20 ml), dried(Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 0.6 g (95 %) of 4-methoxymethoxy-isobenzofuran-1,3-dione as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, J = 8, 1H), 7.62 (d, J = 8, 1H), 7.59 (d, J = 8, 1H), 5.43 (s, 2H), 3.55 (s, 3H).

A mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.15 g, 0.53 mmol) and 4-methoxymethoxy-isobenzofuran-1,3-dione (135 mg, 0.64 mmol) was dissolved in distilled acetonitrile (7 ml) under nitrogen. The flask was

cooled in an ice bath with stirring and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.12 g, 0.64 mmol), and triethylamine (0.22 ml, 1.59 mmol) were added. The reaction was warmed to ambient temperature and stirred for 18 h. The solution was concentrated in vacuo and the residue dissolved in ethyl acetate (40 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (10 ml), and brine (10 ml). The resulting solution was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo which afforded 0.18 g of a crude 2-amino-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester which was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (m, 2H), 7.51 (d, J = 8 , 1H), 6.00-5.86 (2s, 2H), 5.39 (s, 2H), 4.94-4.89 (m, 1H), 4.18-4.02 (m, 2H), 3.86-3.65 (m, 2H), 3.54 (s, 3H), 2.85-2.73 (m, 2H), 1.55 (s, 9H).
APCI-MS: $[M+H]^+$ = 475.4

To a solution of crude 2-amino-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.18 g) in distilled dichloromethane (4 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.23 g, 1.2 mmol). The reaction was stirred for 3 h., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), and brine (5 ml). The resulting solution was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (0 to 5 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 90 mg (28 % in two steps) of 2-(*tert*-butoxyoxalyl-amino)-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 7.64 (t, *J* = 8, 1H), 7.51 (d, *J* = 8, 1H), 7.46 (d, *J* = 8, 1H), 5.40 (s, 2H), 5.11-5.07 (m, 1H), 4.16-4.08 (m, 2H), 3.84-3.72 (m, 2H), 3.55 (s, 3H), 2.95-2.81 (m, 2H), 1.62 (s, 9H), 1.59 (s, 9H).

APCI-MS: $[M+H]^+$ = 603.8

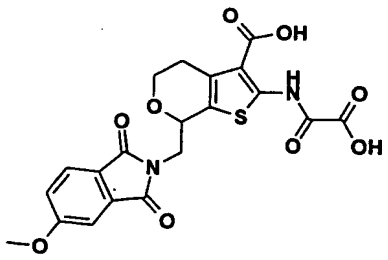
The above 2-(*tert*-butoxyoxalyl-amino)-7-(4-methoxymethoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (86 mg, 0.143 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 55 mg (86 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 11.10 (s, 1H), 7.63 (t, *J* = 8, 1H), 7.31 (d, *J* = 8, 1H), 7.22 (d, *J* = 8, 1H), 4.99-4.95 (m, 1H), 4.05-4.00 (m, 1H), 3.91-3.86 (m, 1H), 3.76-3.66 (m, 2H), 2.88-2.80 (m, 2H).

APCI-MS: $[M+H]^+$ = 447.4

HPLC (254.4 nm): R_t=2.92 min, 100%

EXAMPLE 26



5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

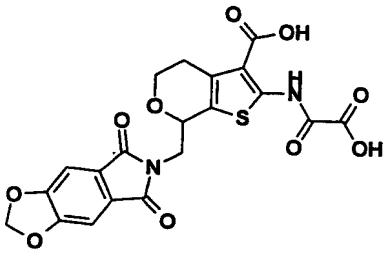
M.p.: 234 - 236 °C;

Calculated for $C_{20}H_{16}N_2O_9S$, 0.25 x H_2O;

C, 51.67 %; H, 3.58 %; N, 6.03 %. Found:

C, 51.95 %; H, 3.92 %; N, 6.06 %.

EXAMPLE 27



7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

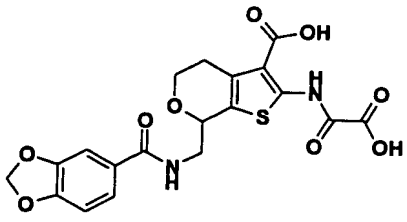
M.p.: 239.5 - 242.5 °C;

Calculated for $C_{20}H_{14}N_2O_{10}S$, 0.1 x H_2O;

C, 50.45 %; H, 3.01 %; N, 5.88 %. Found:

C, 51.06 %; H, 3.43 %; N, 5.93 %.

EXAMPLE 28



7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

Phthalimidoacetaldehyde diethyl acetal (100 g, 0.38 mol) and 1 N hydrochloric acid (600 ml) was mixture was stirred at reflux temperature for 5 min. or until a homogeneous solution is obtained. The reaction mixture was cooled and the precipitate was filtered off and dried in vacuo at 50 °C for 16 h which afforded 63.3 g (88 %) of phthalimido-acetaldehyde as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2H), 7.76 - 7.78(m, 2H), 7.90 - 7.92 (m, 2H), 9.67 (s, 1H).

To a mixture of phthalimidoacetaldehyde (64 g, 0.34 mol) and trans-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (81.5 g, 0.38 mol) in benzene (600 ml) stirred for 15 min. under nitrogen was added dropwise a 45 % solution of zinc chloride diethyl ether complex in dichloromethane (55.5 ml, 0.17 mol) at 0 °C. The reaction was allowed warm up to room temperature overnight. To the reaction mixture was added water (500 ml) and the resulting mixture was extracted with ethyl acetate (200 ml). The organic extract was washed successively with 1.0 N hydrochloric acid (2 x 200 ml) and brine (200 ml). The organic phase was dried (Na_2SO_4), filtered and the solvent evaporated in vacuo which afforded a slowly crystallising oil (98 g). To the solid was added a mixture of ethyl acetate and diethyl ether (400 ml, 1:1) and the resulting precipitate was filtered off, washed with a small portion of diethyl ether and dried at 50 °C for 1h affording 59.8 g (69 %) of 2-(4-oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid. The filtrate was evaporated in vacuo and the residue purified by column chromatography on silica gel (1 L) using a mixture of ethyl acetate and heptane (1:2) as eluent. Pure fractions were collected and the solvent evaporated in vacuo to almost dryness, the solid was filtered off and dried in vacuo at 50 °C for 16 h affording an additional 15 g (17 %) of 2-(4-oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (d, 2H), 3.85 (dd, 1H), 4.18 (dd, 1H), 4.76 (m, 1H), 5.43 (d, 1H), 7.28 (d, 1H), 7.69 - 7.77 (m, 2H), 7.84 - 7.88 (m, 2H).

2-(4-Oxo-3,4-dihydro-2H-pyran-2-ylmethyl)-isoindole-1,3-dione (13 g, 0.051 mol) was dissolved in ethyl acetate (250 ml) and placed in a Parr bottle. 10 % Pd/C (1.5 g) was carefully added and the mixture was shaken under a pressure of 30 psi of hydrogen for 6.5 h (Parr apparatus). Filtration followed by evaporation of the ethyl acetate in vacuo afforded a crude 11.5 g of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione pure enough for the next step. Analytical pure compound could be obtained by purification of a small sample (250 mg) by column chromatography on silica gel, utilising a mixture of hexane/ethyl acetate as a gradient (from 100/0 to 50/50). Pure fractions were collected and the solvent evaporated in vacuo affording 142 mg (55 %) of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione as a solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 - 2.68 (m, 4H), 3.62 (m, 1H), 3.74 (m, 1H), 4.00 (m, 2H), 7.75 (m, 2H), 7.88 (m, 2H).

To a mixture of 2-(4-oxo-tetrahydro-pyran-2-ylmethyl)-isoindole-1,3-dione (11.5 g, 44 mmol), *tert*-butyl cyanoacetate (6.9 g, 49 mmol) and elemental sulfur (1.6 g, 49 mmol) in ethanol (250 ml) was added morpholin (15 ml) and the resulting mixture was stirred at 50 °C for 16 h. The cooled reaction mixture was filtered and the precipitate filtered off and washed with diethyl ether and dried in vacuo affording 6.5 g (35 %) of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
The filtrate was evaporated in vacuo and the residue was dissolved in ethyl acetate (200 ml) washed with water (2 x 100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo affording 6.0 g (33 %) of almost regioisomer pure 2-amino-7-(1,3-dioxo-1,3-dihydro-

isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.54 - 2.63 (m, 1H), 2.84 - 2.90 (m, 1H), 3.79 (q, 1H), 3.96 - 4.04 (m, 2H), 4.48 - 4.62 (m, 2H), 5.91 (bs, 2H, NH_2), 7.70 (m, 2H), 7.84 (m, 2H).

2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.71 - 2.90 (m, 2H), 3.67 - 3.77 (m, 2H), 4.02 - 4.15 (m, 2H), 4.90 (m, 1H), 6.04 (bs, 2H, NH_2), 7.70 (m, 2H), 7.84 (m, 2H).

To a solution of 2-amino-7-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (6.0 g, 0.014 mol) in ethanol (100 ml) was added hydrazine-hydrate (1.4 ml, 0.029 mol). The mixture was stirred at reflux temperature for 1 h. The cooled reaction mixture was filtered and the solvent evaporated in vacuo. The residue was dissolved in diethyl ether (200 ml) and washed with water (100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo affording 2.9 g (71 %) of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

To a ice cooled mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1.4 g, 4.92 mmol), triethylamine (2 ml) in dichloromethane (100 ml) was added dropwise a solution of benzo[1,3]dioxole-5-carbonyl chloride (1.0 g, 5.41 mmol) in dichloromethane (25 ml) during 1.5 h. The ice cooled reaction mixture was stirred for an additional 0.5 h. The volatiles were evaporated in vacuo and the residue was dissolved in ethyl acetate (200 ml) and washed with water

(2 x 100 ml), brine (100 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (2 g) was subjected to flash column chromatography (1 l silicagel) using a mixture of ethyl acetate/hexane (1:2) as eluent. Pure fractions were collected affording after evaporation in vacuo 0.3 g (14 %) of 2-amino-7-(((benzo[1,3]dioxole-5-carbonyl)amino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

TLC: R_f = 0.44 (ethyl acetate/heptane 1:1)

A mixture of the above 2-amino-7-(((benzo[1,3]dioxole-5-carbonyl)amino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 0.69 mmol), imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.16 g, 0.83 mmol) in dry tetrahydrofuran (50 ml) was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue was dissolved in ethyl acetate (100 ml) and washed with water (2 x 50 ml), brine (50 ml), dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The residue (0.35 g) was subjected to flash column chromatography (500 ml silicagel) using a mixture of ethyl acetate/hexane (1:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo. The residue was trituated with diethyl ether (5 ml), filtered off and dried in vacuo at 50 °C for 5 h which afforded 0.17 g (44 %) of 7-(((benzo[1,3]dioxole-5-carbonyl)amino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

TLC: R_f = 0.37 (ethyl acetate/heptane 1.1).

The above di-*tert*-butyl ester (0.17 g, 0.30 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (20 ml). The reaction was stirred at room temperature for 5.5 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (10 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 72 h which afforded 100 mg (74 %) of the title compound as a solid.

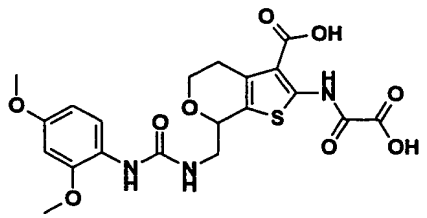
M.p.: 227 - 230° C;

Calculated for $C_{19}H_{16}N_2O_9S$, 0.5 x H_2O;

C, 49.89 %; H, 3.75 %; N, 6.12 %. Found:

C, 50.02 %; H, 3.68 %; N, 5.98 %.

EXAMPLE 29



7-[3-(2,4-Dimethoxy-phenyl)-ureidomethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (64 mg, 0.22 mmol) in dichloromethane (1 ml) was added 2,4-dimethoxyphenylisocyanate (40 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, diluted with ethyl acetate (30 ml), washed with saturated sodium carbonate (3 x 25 ml), brine (3 x 25 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was subjected to preparative thin layer chromatography (100% dichloromethane). R_f=0.8 was isolated and the solvent evaporated in vacuo which afforded 55 mg (53 %) of 2-amino-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.6, 1H), 7.62 (d, *J* = 8.1, 1H), 6.45 (m, 3H), 5.00 (bs, 2H), 4.68 (m, 1H), 4.12 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.76-3.67 (m, 1H), 3.30 (dd, *J* = 14, 6.9, 1H), 2.76 (m, 2H), 1.55 (s, 9H).

MS: APCI (+): 464.3 (M+H).

To a solution of the above 2-amino-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (47 mg, 0.11 mmol) in dichloromethane (1 ml) was added triethylamine (28 µl, 0.22 mmol) and midazol-1-yl-oxo-acetic acid *tert*-butyl ester (40 mg, 0.22 mmol). The mixture allowed to stir at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue diluted with ethyl acetate (35 ml). The organic phase was washed with saturated sodium carbonate (3 x 25 ml), brine (3 x 25 ml), dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography (60 % ethyl acetate/40 % hexanes). Pure 2-(*tert*-butoxyoxalyl-amino)-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester 34 mg (58 %) was isolated as an oil.

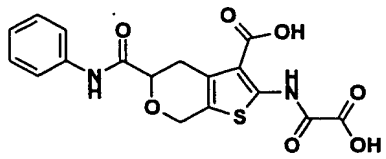
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.70 (d, *J* = 9.6, 1H), 6.62 (bs, 1H), 6.47 (m, 3H), 5.02 (bs, 1H), 4.84 (m, 1H), 4.19 (dm, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75-3.70 (m, 1H), 3.36 (dd, *J* = 13.5, 7.5, 1H), 2.87 (m, 2H), 1.61 (s, 9H), 1.60 (s, 9H).

MS: APCI (+): 592.4 (M+H).

The above 2-(*tert*-butoxyoxalyl-amino)-7-(3-(2,4-dimethoxy-phenyl)ureidomethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (34 mg) was dissolved in 20 % trifluoroacetic acid in dichloromethane (2 ml) and stirred at room temperature for 3 h. The volatiles were evaporated in vacuo and the residue was titurated with diethyl ether (2x), filtered off and washed with a small amount of dichloromethane which afforded after drying in vacuo 16 mg (89 %) of the title compound as a solid.

^{1}H NMR (300 MHz, CD_3OD) δ 7.66 (d, *J* = 9, 1H), 6.53 (d, *J* = 2.7, 1H), 6.44 (dd, *J* = 9, 2.7, 2H), 4.82 (m, 1H), 4.2 (m, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.67 (dd, *J* = 13, 4.5, 2H), 2.94 (m, 2H).
MS: APCI (+): 480.3 (M+H);

EXAMPLE 30



2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

A solution of glyoxylic acid ethyl ester, polymer form (2.02 g, 8.9 mmol) and (3-methoxy-1-methylene-allyloxy)-trimethyl-silane (1.9 ml, 8.9 mmol, Danishefsky's diene) in benzene (12 ml) was placed under nitrogen. Zinc chloride (0.5N in tetrahydrofuran, 8.9 ml, 4.45 mmol) was added and the reaction stirred at ambient temperature for 72 h. The mixture was concentrated in vacuo, diluted with ethyl acetate (100 ml) and washed with 1N hydrochloric acid (20 ml), saturated sodium bicarbonate (20 ml), and brine (20 ml). The organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a mixture of ethyl acetate/hexane (1:2) as eluent. Pure fractions were collected and the solvent evaporated in vacuo which afforded 1.2 g (75 %) of 4-oxo-3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 6, 1H), 5.48 (d, *J* = 6, 1H), 5.01 (t, *J* = 8, 1H), 4.28 (q, *J* = 7, 2H), 2.85 (d, *J* = 8, 2H), 1.29 (t, *J* = 7, 3H).

To a solution of the above of 4-oxo-3,4-dihydro-2H-pyran-2-carboxylic acid ethyl ester (1.0 g, 5.9 mmol) in ethyl acetate (12 ml) was added 10 % palladium on activated carbon (0.15 g). The reaction was shaken on a

Parr hydrogenator under a hydrogen atmosphere (30 psi) for 1.5 h. The mixture was filtered through celite and concentrated in vacuo. The residue was purified by silica gel chromatography using diethyl ether as eluent. Pure fractions were collected and the solvent evaporated in vacuo which affording 0.6 g (60 %) of 4-oxo-tetrahydro-2H-pyran-2-carboxylic acid ethyl as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41-4.35 (m, 1H), 4.26 (q, *J* = 7, 2H), 3.81-3.70 (m, 1H), 2.73-2.58 (m, 3H), 2.44-2.36 (m, 1H), 1.29 (t, *J* = 7, 3H).

To a solution of 4-oxo-tetrahydro-2H-pyran-2-carboxylic acid ethyl (0.6 g, 3.5 mmol) in absolute ethanol (6 ml) was added sulfur (0.12 g, 3.85 mmol) and *tert*-butyl cyanoacetate (0.64 g, 4.55 mmol). The solution was stirred under nitrogen in a 50 °C oil bath and morpholin (0.61 ml, 7.0 mmol) was added. The reaction was stirred for 18 h. and then cooled to ambient temperature and excess sulfur removed by filtration. The filtrate was concentrated in vacuo and reconstituted in ethyl acetate (50 ml). The organic phase was washed with brine (2 x 10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was purified by silica gel chromatography using a gradient of ethyl acetate/hexane (20 to 25 % gradient) as eluent. Pure fraction of the two isomers were collected and the solvent evaporated in vacuo which afforded 0.47 g of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester 5-ethyl ester (**A**) and 0.3 g of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (B) in 62 % combined yield.

(A)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (bs, 2H), 4.77-4.61 (m, 2H), 4.32-4.18 (m, 3H), 3.19-3.12 (m, 1H), 2.90-2.80 (m, 1H), 1.52 (s, 9H), 1.29 (t, *J* = 7, 3H).

APCI-MS: $[M+H]^+$ = 272.4 (loss of t-butyl)

(B)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (s, 1H), 4.28-4.13 (m, 3H), 3.98-3.91 (m, 1H), 2.82-2.76 (m, 2H), 1.51 (s, 9H), 1.31 (t, *J* = 7, 3H).

APCI-MS: $[M+H]^+$ = 272.4 (loss of t-butyl)

The above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester 5-ethyl ester (275 mg, 0.84 mmol) was dissolved in a mixture of ethanol (4 ml) and tetrahydrofuran (1 ml). Sodium hydroxide (1N, 1.6 ml, 1.68 mmol) was added and the reaction stirred at ambient temperature for 5 h. after which TLC analysis indicated that the reaction was complete. The reaction was monitored with a pH meter and neutralized with 1N hydrochloric acid until pH = 6.9. The solution was concentrated in vacuo to give 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester as a solid. Sodium chloride remained as an impurity.

^{1}H NMR (300 MHz, CD_3OD) δ 4.67-4.54 (m, 2H), 4.00-3.95 (m, 1H), 3.20-3.12 (m, 1H), 2.74-2.63 (m, 1H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 300.0

To a solution of the above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester (94 mg, 0.31 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (72 mg, 0.37 mmol) in distilled dichloromethane (4 ml) under nitrogen was added aniline (32 μl, 0.34 mmol) followed by 2,6-lutidine (0.11 ml, 0.93 mmol). The reaction was stirred for 72 h., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1% hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml), brine (10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo to give 51 mg (45 %) of 2-amino-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.60 (d, 1H, *J* = 7), 7.49 (d, 1H, *J* = 8), 7.34 (t, 1H, *J* = 8), 7.32 (t, 1H, *J* = 8), 7.13 (t, 1H, *J* = 7), 6.03 (s,

2H), 4.82-4.73 (m, 2H), 4.25-4.22 (m, 1H), 3.43-3.38 (m, 1H), 2.79-2.72 (m, 1H), 1.54 (s, 9H).
APCI-MS: $[M+H]^+$ = 375.5

To a solution of the above 2-amino-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (51 mg, 0.14 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (80 mg, 0.42 mmol) and triethylamine (38 µl, 0.28 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 4 % mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 41 mg (26 % over two steps) of 2-(*tert*-butoxyoxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.40 (s, 1H), 7.59 (d, *J* = 8, 2H), 7.33 (t, *J* = 8, 2H), 7.12 (t, *J* = 7, 1H), 5.01-4.85 (m, 2H), 4.27-4.22 (m, 1H), 3.54-3.47 (m, 1H), 3.89-2.79 (m, 1H), 1.60 (s, 9H), 1.58 (s, 9H).
APCI-MS: $[M+H]^+$ = 503.2

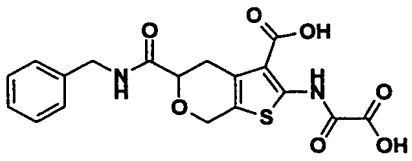
The above 2-(*tert*-butoxyoxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (37 mg, 0.074 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with ethyl ether and dried in vacuo to give 18 mg (62 %) of the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.85 (s, 1H), 7.69 (d, *J* = 8, 2H), 7.31 (t, *J* = 8, 2H), 7.07 (t, *J* = 7, 1H), 4.98 (d, *J* = 15, 1H), 4.83 (d, *J*

= 15, 1H), 4.35-4.31 (m, 1H), 3.23 (d, *J* = 17, 1H), 2.84 (dd, *J* = 17, 10, 1H).

APCI-MS: $[M+H]^+$ = 391.3

HPLC (254.4nm): R_t=3.22 min, 100%

EXAMPLE 31



5-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,5-dicarboxylic acid 3-*tert*-butyl ester (101 mg, 0.34 mmol, prepared in Example 31) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (78 mg, 0.41 mmol) in distilled dichloromethane (4 ml) under nitrogen was added benzylamine (40 µl, 0.37 mmol) followed by 2,6-lutidine (0.12 ml, 1.02 mmol). The reaction was stirred for 72 h., concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1 % hydrochloric acid (10 ml), saturated sodium bicarbonate (10 ml), brine (10 ml), dried (Na_2SO_4) over sodium sulfate, filtered, and the solvent evaporated in vacuo to give 72 mg (56 %) of 2-amino-5-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.66 (s, 2H), 4.44 (d, *J* = 5, 2H), 4.17-4.13 (m, 1H), 3.40-3.33 (m, 1H), 2.75-2.66 (m, 1H), 1.54 (s, 9H).

APCI-MS: $[M+H]^+$ = 389.5

To a solution of the above 2-amino-5-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester (72 mg, 0.19 mmol) in

distilled dichloromethane (4 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.57 mmol) and triethylamine (51 µl, 0.38 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (25 ml). The organic layer was washed with 1% hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a gradient of ethyl acetate/dichloromethane (5 to 10 % gradient) as eluent. Pure fractions were collected and the solvent evaporated in vacuo to give 42 mg (24 % over two steps) of 5-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 7.37-7.29 (m, 5H), 6.97 (t, 1H, *J* = 6), 4.89-4.77 (m, 2H), 4.58-4.46 (m, 2H), 4.20-4.16 (m, 1H), 3.50-3.44 (m, 1H), 2.84-2.76 (m, 1H), 1.61 (s, 9H), 1.60 (s, 9H).

APCI-MS: $[M+H]^+$ = 517.3

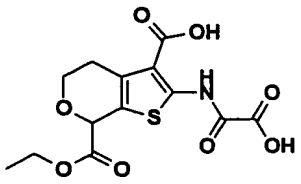
The above 5-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,carboxylic acid *tert*-butyl ester (36 mg, 0.07 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (3 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 14 mg (50 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.48 (t, *J* = 6, 1H), 7.31-7.20 (m, 5H), 4.91 (d, *J* = 15, 1H), 4.76 (d, *J* = 15, 1H), 4.32-4.29 (m, 2H), 4.20-4.16 (m, 1H), 3.22 (m, 1H, partially obscured by water), 2.70-2.63 (m, 1H).

APCI-MS: $[M+H]^+$ = 405.2

HPLC (254.4nm): R_t=3.06 min, 100%

EXAMPLE 32



2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (60 mg, 0.18 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.54 mmol) and triethylamine (50 µl, 0.36 mmol). The reaction was stirred for 4 h., concentrated in vacuo and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 6 % mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 78 mg (95 %) of 2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.54 (s, 1H), 5.28 (s, 1H), 4.27 (q, 2H, *J* = 7), 4.25-4.18 (m, 1H), 4.04-3.96 (m, 1H), 2.96-2.80 (m, 2H), 1.60 (s, 9H), 1.57 (s, 9H).

LC-MS: R_t=3.97 min, $[M+H]^+$ = 456.3

The above 2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (72 mg, 0.16 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (4 ml). The reaction was stirred at ambient temperature for 7 h.,

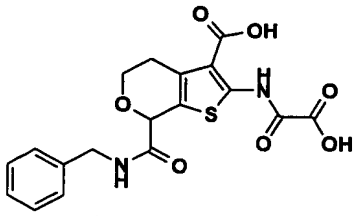
concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 48 mg (88 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 5.47 (s, 1H), 4.19 (q, J = 7, 2H), 3.98-3.94 (m, 2H), 2.90-2.78 (m, 2H), 1.23 (t, J = 7, 3H).

APCI-MS: $[M+H]^+$ = 344.2

HPLC (254.4nm): R_t=2.82 min, 100%

EXAMPLE 33



7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester 7-ethyl ester (0.12 g, 0.37 mmol) in ethanol (3 ml) was added potassium hydroxide (56 mg, 1.0 mmol) dissolved in a minimum amount of water. The mixture was stirred for 24 h., then 1N hydrochloric acid was added until pH = 7. The solution was concentrated in vacuo and the residue partitioned between ethyl acetate (35 ml) and water (10 ml). The layers were separated and 1 % hydrochloric acid (1 ml) was added to the aqueous layer. The aqueous layer was then extracted further with ethyl acetate (3 x 15 ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and filtered. Triethylamine (3 drops) was added to the solution to stabilize the acid-sensitive compound. The solution was concentrated in vacuo affording 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester triethylamine salt (approximately 0.13 g) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.28-4.23 (m, 1H), 3.90-3.85 (m, 1H), 2.88-2.71 (m, 3H), 1.56 (s, 9H).

A solution of the above 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 3-*tert*-butyl ester triethylamine salt (0.12 g, 0.30 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (71 mg, 0.36 mmol) was prepared in distilled acetonitrile under nitrogen. Benzylamine (36 µl, 0.33 mmol) was added followed by 2,6-lutidine (70 µl, 0.60 mmol). The reaction was stirred at ambient temperature for 18 h., then concentrated in vacuo and reconstituted in ethyl acetate (30 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 5 ml), and brine (10 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo which afforded crude 2-amino-7-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester which was used without purification.

To a solution of the above crude 2-amino-7-benzylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (77 mg, 0.2 mmol) in distilled dichloromethane (3 ml) under nitrogen was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.11 g, 0.6 mmol) and triethylamine (55 µl, 0.4 mmol). The reaction was stirred for 5 h., concentrated in vacuo and reconstituted in ethyl acetate (20 ml). The organic layer was washed with 1 % hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (5 ml), brine (5 ml), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The crude material was purified by silica gel chromatography using a 5 % mixture of ethyl acetate/dichloromethane as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 29 mg (19 % over two steps) of 7-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.35-7.26 (m, 5H), 6.96 (t, J = 6, 1H), 5.20 (s, 1H), 4.55-4.41 (m, 2H), 4.22-4.17 (m, 1H), 3.87-3.81 (m, 1H), 2.97-2.84 (m, 2H), 1.61 (s, 9H), 1.59 (s, 9H).

APCI-MS: $[M-H]^-$ = 516

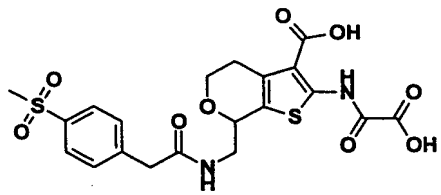
The above 7-benzylcarbamoyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (29 mg, 0.06 mmol) was dissolved in a solution of 50 % trifluoroacetic acid/dichloromethane (2 ml). The reaction was stirred at ambient temperature for 7 h., concentrated in vacuo and the residue evaporated in vacuo from dichloromethane (3 x 10 ml). The resulting precipitate was washed with dichloromethane and dried in vacuo to give 18 mg (80 %) of the title compound as an solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.67 (t, *J* = 6, 1H), 7.30-7.21 (m, 5H), 5.23 (s, 1H), 4.31-4.28 (m, 2H), 4.13-4.10 (m, 1H), 3.88-3.85 (m, 1H), 2.86 (bs, 2H).

APCI-MS: $[M+H]^+$ = 405

HPLC (254.4nm): R_t=3.12 min, 94 %

EXAMPLE 34



7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of (4-methanesulfonyl-phenyl)-acetic acid (90.4 mg, 0.42 mmol) in a mixture of dichloromethane (3 ml) and N,N-dimethylformamide (1 ml) cooled at 0 °C was added diisopropyl-ethylamine (306 µl, 1.76 mmol), diisopropylazodicarboxylate (72 µl, 0.45 mmol) and 1-hydroxy-benzotriazole (56.6 mg, 0.42 mmol). After being stirred for 20 minutes, 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (100 mg, 0.35

mmol) dissolved in dichloromethane (1 ml) was added via syringe. The reaction mixture was stirred for 18 h. while slowly warming to room temperature. The volatiles were evaporated in vacuo and the residue diluted with ethyl acetate (50 ml). The organic phase was washed with saturated sodium bicarbonate (3 x 50 ml), 1 % hydrochloric acid (3 x 50 ml), brine (3 x 50 ml),dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9) as eluent. Fraction with R_f=0.5 was isolated which afforded after evaporating the solvent in vacuo 115 mg (69 %) of 2-amino-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.7, 2H), 7.39 (d, *J* = 7.5, 2H), 5.91 (bs, 2H), 4.65 (m, 1H), 4.09 (dt, J = 7.8, 3.3, 1H), 3.85-3.65 (m, 2H), 3.61 (s, 2H), 3.45-3.38 (m, 2H), 3.05 (s, 3H), 2.75 (m, 2H), 1.56 (s, 9H).

MS: APCI (+): 481 (M+H).

To a solution of the above 2-amino-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (110 mg, 0.23 mmol) in dichloromethane (3 ml) was added triethylamine (96 µl, 0.69 mmol) and midazol-1-yl-oxo-acetic acid *tert*-butyl ester (134 mg, 0.69 mmol). The reaction was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo, diluted in ethyl acetate (50 ml), washed with saturated sodium carbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The resultant oil was subjected to preparative thin layer chromatography using a mixture of methanol/dichloromethane (1:9). Fraction with R_f=0.5 was collected and the solvent evaporated in vacuo affording 70 mg (50 %) of 2-(*tert*-butoxyoxalyl-amino)-7-((2-(4-methanesulfonyl-

phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.88 (d, *J* = 8.1, 2H), 7.46 (d, *J* = 8.1, 2H), 5.88 (bs, 1H), 4.78 (m, 1H), 4.15 (dt, *J* = 12, 4, 1H), 3.86-3.71 (m, 2H), 3.64 (s, 2H), 3.42-3.34 (m, 2H), 3.04 (s, 3H), 2.85 (m, 2H), 1.62 (s, 9H), 1.61 (s, 9H).

MS: APCI (+): 609 (M+H)[minor], 497 (-2 *tert* butyls)[major];

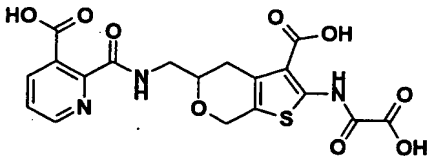
LC-MS: s, 99 %

The above 2-(*tert*-butoxyoxalyl-amino)-7-((2-(4-methanesulfonyl-phenyl)acetylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (60 mg, 0.098 mmol) was dissolved in 50 % trifluoroacetic acid in dichloromethane (2 ml) and allowed to stir at room temperature for 3 h. The reaction mixture was concentrated in vacuo, the residue titurated with diethyl ether (3x), and dried in vacuo which afforded 45 mg (92 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.47 (m, 1H), 7.82 (d, *J* = 7.8, 2H), 7.50 (d, *J* = 7.8, 2H), 4.75 (bs, 1H), 4.10 (m, 1H), 3.69 (m, 1H), 3.60 (d, *J* = 3.6, 2H), 3.52 (m, 1H), 3.35 (m, 2H), 3.18 (s, 3H), 2.83 (m, 2H).

MS: APCI (-): 495 (M-H); LC-MS: s, 95 %.

EXAMPLE 35



2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid

2-(*tert*-Butoxyoxalyl-amino)-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (164 mg, 0.58 mmol) was stirred

for 20 h at 80 °C with furo[3,4-b]pyridine-5,7-dione (86.1 mg, 0.58 mmol) in a mixture of tetrahydrofuran (1.0 ml) and N,N-dimethylformamide (0.25 ml). The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate (50 ml) and washed with water (3 x 30ml). The organic layer was dried($MgSO_4$), filtered, and the solvent evaporated in vacuo. The residue (78 mg) was purified by preparative TLC (hexane/ethyl acetate, 50:50) which afforded 2 products: 2-((2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid **(A)** (27.9 mg, 11 %) and 2-amino-5-(5,7-dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (**B**) (21.3 mg, 9 %).

(A)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.74 (d, *J* = 3.3, 1H), 8.14 (d, *J* =7.5, 1H), 7.40 (dd, *J* = 4.8, *J* = 5.1, 1H), 6.71 (m, 1H), 5.98 (s, 2H), 4.63 (s, 2H), 4.00 (m, 1H), 3.42 (m, 1H), 2.90 (dd, *J* = 3.3, *J* = 3.6, 1H), 2.59 (dd, *J* = 11, *J* = 11, 1H), 1.48 (s, 9H).

MS *m/z* 434 (M+);

(B)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, *J* = 5.1, 1H), 8.20 (d, *J* = 9, 1H), 7.64 (dd, *J* = 5.7, 4.8, 1H), 5.94 (s, 2H), 4.60 (d, *J* = 14, 1H), 4.51 (d, *J* = 14, 1H), 4.05 (m, 2H), 3.87 (d, *J* = 12.5, 1H), 2.92 (d, *J* = 17, 1H), 2.61 (m, 1H), 1.53 (s, 9H).

MS: APCI (+): 416 (M+1)[minor], 360 (M- *tert*-butyl) [major].

To a solution of the above 2-((2-amino-3-*tert*-butoxycarbonyl-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid (27.9 mg, 0.064 mmol) in tetrahydrofuran (2 ml) was added midazol-1-yl-oxo-acetic acid *tert*-butyl ester (38 mg, 0.193 mmol) and triethylamine (9 µl, 0.064 mmol). The resulting mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (20 ml) and washed with water (3 x 10 ml). The extracts

were dried($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was purified by preparative TLC (0.5mm, hexane/ethyl acetate, 1/1 to 2/3 gradient). After evaporation of the solvent in vacuo 917 mg (46 %) of 2-(3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid was isolated as a solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.75 (s, 1H), 8.15 (d, *J* = 7.5, 1H), 7.42 (dd, *J* = 6.9, *J* = 5.1, 1H), 6.73 (m, 1H), 4.81 (dd, *J* = 15.3, *J* = 14.4, 2H), 4.03 (m, 1H), 3.83 (m, 1H), 3.47 (m, 1H), 2.99 (d, *J* = 17.1, 1H), 2.59 (dd, *J* = 11.1, *J* = 10.8, 1H), 1.61 (s, 9H), 1.48 (s, 9H).

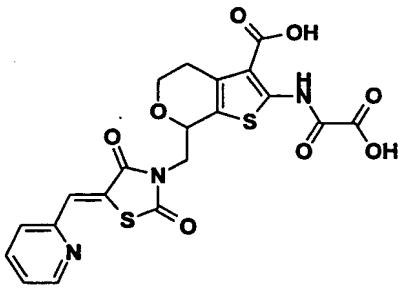
MS: 506 (M-55).

The above 2-(3-*tert*-butoxycarbonyl-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)carbamoyl)nicotinic acid (13.1 mg, 0.023 mmol) was stirred in 50 % trifluoroacetic acid in dichloromethane (2 ml) at room temperature for 7 h. The solvent was evaporated in vacuo which afforded 10 mg (96 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.77 (d, *J* = 7.7, 1H), 8.16 (d, *J* = 7.5, 1H), 7.60 (d, *J* = 7.8, 1H), 4.88 (d, *J* = 9, 1H), 4.76 (d, *J* = 9, 1H), 3.96 (m, 1H), 3.02 (m, 1H), 2.78 (m, 1H).

MS: 481 (M+33).

EXAMPLE 36



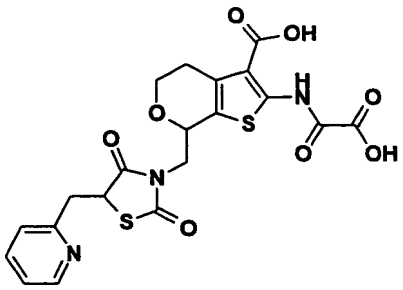
7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (1.0 g, 2.42 mmol), 5-pyridin-2-ylmethylene-thiazolidine-2,4-dione (0.55 g, 2.66 mmol, prepared in a similar way as described in J. *Med. Chem.* **41** (10), 1619-1630 (1998)) and triphenylphosphine (0.7 g, 2.66 mmol) in dry tetrahydrofuran (75 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (420 µl ml, 2.66 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo, the resultant solid was washed with diethyl ether, filtered off and dried in vacuo at 50 °C for h affording 1.4 g (96 %) of 2-(*tert*-butoxyoxalyl-amino)-7-(2,4-dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
TLC: R_f = 0.46 (ethyl acetate/heptane 1:1).

The above di-*tert*-butyl ester (1.0 g, 1.66 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (30 ml). The reaction was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (50 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 16 h which afforded 0.8 g of semi pure title compound. The title compound (0.8 g) was suspended in ethyl acetate (25 ml) and heated at reflux temperature for 0.5 h. Isopropanol (5 ml) was added and the mixture was cooled to room temperature the precipitate filtered off and dried in vacuo at 50 °C for 16 h which afforded 0.37 g (37 %) of the title compound as a solid.

Calculated for $C_{20}H_{15}N_3O_8S_2$, 0.5 x H_2O, 0.75 x isopropanol;
C, 49.17 %; H, 4.08 %; N, 7.73 %. Found:
C, 48.97 %; H, 4.03 %; N, 7.45 %.

EXAMPLE 37



7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 5-pyridin-2-ylmethylene-thiazolidine-2,4-dione (5.0 g, 0.024 mol, prepared in a similar way as described in J. *Med. Chem.* **41** (10), 1619-1630 (1998)) in tetrahydrofuran (300 ml) was added 10 % palladium on carbon (1 g) and the resulting mixture was hydrogenated. After 50 ml of hydrogen was consumed and additional portion of 10 % palladium on carbon (5 g) was added and the hydrogenation was continued at 50 psi for 16 h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was subjected to flash column chromatography (1 l silicagel) using a mixture of ethyl acetate/hexane (1:1) as eluent. Semi pure fractions were collected and the solvent evaporated in vacuo affording 0.8 g (16 %) of 5-pyridin-2-ylmethyl-thiazolidine-2,4-dione as a solid.

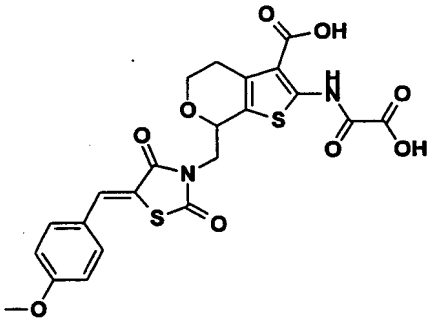
To a mixture of 2-(*tert*-butoxyoxalyl-amino)-7-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.7 g, 1.69 mmol), 5-pyridin-2-ylmethyl-thiazolidine-2,4-dione (0.36 g, 1.86 mmol) and triphenylphosphine (0.49 g, 1.86 mmol) in dry tetrahydrofuran (40 ml) cooled to 0 °C under a nitrogen atmosphere was added diethyl azodicarboxylate (DEAD) (290 µl ml, 1.86 mmol). The reaction mixture was allowed to stir overnight, slowly warming to room temperature. The volatiles were evaporated in vacuo, the resultant residue was subjected to flash column chromatography (0.5 l silicagel) using a mixture of ethyl acetate/hexane (1:2) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.6 g (59 %) of 2-(*tert*-butoxyoxalyl-

amino)-7-(2,4-dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid. TLC: R_f = 0.43 (ethyl acetate/heptane 1:1).

The above di-*tert*-butyl ester (0.5 g, 0.83 mmol) was dissolved in 25 % trifluoroacetic acid in dichloromethane (25 ml). The reaction was stirred at room temperature for 16 h. The volatiles were evaporated in vacuo and the residue trituated with diethyl ether (20 ml). The precipitate was filtered off, washed with diethyl ether, dried in vacuo at 50 °C for 1 h which afforded 0.3 g of semi pure title compound. The title compound (0.3 g) was suspended in isopropanol (15 ml) and heated at reflux temperature for 5 min., cooled to room temperature and the precipitate filtered off and dried in vacuo at 50 °C for 16 h which afforded 0.2 g (49 %) of the title compound as a solid.

M.p.: > 250 °C;
Calculated for $C_{20}H_{17}N_3O_8S_2$, 0.25 x H_2O;
C, 48.43 %; H, 3.56 %; N, 8.47 %. Found:
C, 48.41 %; H, 3.57 %; N, 8.10 %.

EXAMPLE 38



7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

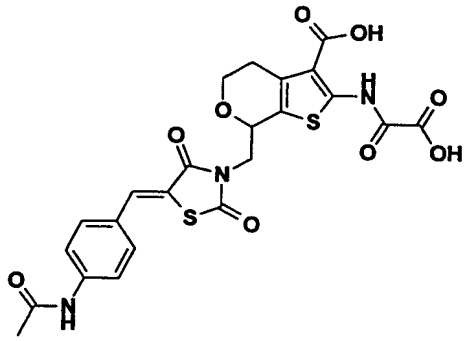
M.p.: 236 - 238 °C;

Calculated for $C_{22}H_{18}N_3O_9S_2$, 0.5 x H_2O;

C, 50.09 %; H, 3.63 %; N, 5.31 %. Found:

C, 49.92 %; H, 3.59 %; N, 5.18 %.

EXAMPLE 39



7-[5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

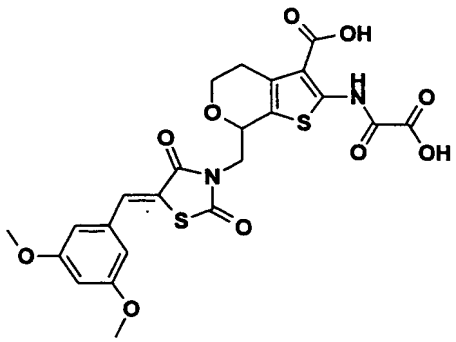
M.p.: > 250 °C;

Calculated for $C_{23}H_{19}N_3O_9S_2$, 2 x H_2O;

C, 47.50 %; H, 3.99 %; N, 7.23 %. Found:

C, 47.60 %; H, 3.45 %; N, 6.80 %.

EXAMPLE 40

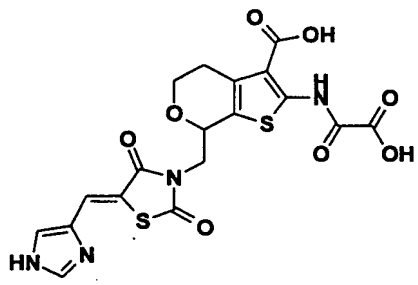


7-[5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.92 (s, 1H), 6.80 (d, *J* = 1.8, 2H), 6.66 (t, *J* = 2.1, 1H), 5.00 (m, 1H), 4.06 (bm, 2H), 3.81 (s, 6H), 3.71 (dd, *J* = 6.6, 6, 2H), 2.83 (m, 2H).
MS: APCI (+): 549 (M+H); LC-MS; s, 90 %.

EXAMPLE 41



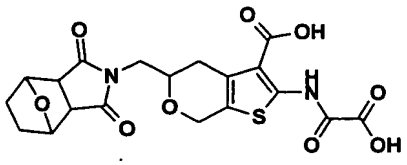
7-[5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 37.

M.p.: > 250 °C;

Calculated for $C_{18}H_{14}N_4O_8S_2$;
C, 40.65 %; H, 2.56 %; N, 9.17 %. Found:
C, 40.54 %; H, 2.55 %; N, 9.46 %.

EXAMPLE 42



5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-hydroxymethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.20 g, 0.48 mmol) in tetrahydrofuran (5 ml) was added 10-oxa-4-aza-tricyclo(5,2,1,0,2,6)decane-3,5-dione (81 mg, 0.48 mmol) and triphenylphosphine (126 mg, 0.48 mmol). The mixture was cooled to 0 °C and diisopropylazodicarboxylate (94.5 µl, 0.48 mmol) was added via syringe. The reaction was stirred for 18h. while slowly warming to room temperature. The volatiles were evaporated in vacuo, and the residue diluted into ethyl acetate (50 ml), washed with saturated sodium bicarbonate (3 x 50 ml), brine (3 x 50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The semi-solid residue was subjected to preparative thin layer chromatography using a mixture of ethyl acetate/hexanes (4:1) as eluent. Fraction with R_f=0.68 was isolated which afforded 64 mg (24 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as a solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.47 (s, 1H), 4.89 (m, 2H), 4.80-4.61 (m, 2H), 3.93-3.86 (m, 1H), 3.83-3.79 (m, 1H), 3.62-3.57 (dd, *J* = 12.6, 3.6, 1H), 2.92 (q, 6.9, 2H), 2.60 (dd, *J* =17.1, 10.5, 2H), 1.85 (m, 2H), 1.60 (s, 18H).

MS: APCI (-): 561 (M-H).

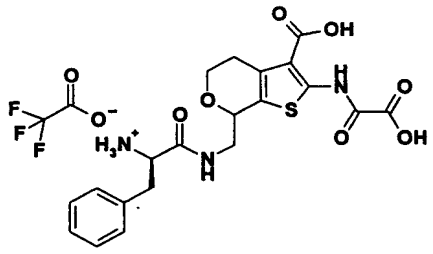
The above 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (51 mg) was dissolved in 50% trifluoroacetic acid in dichloromethane (5ml) and stirred at room temperature for 2 h. The reaction mixture was evaporated in vacuo and the residue titurated with diethyl ether (3 x 10 ml). The solid was filtered of and dried affording 30 mg (71 %) of the title compound as a solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 12.31 (s, 1H), 7.68 (bs, 1H), 4.69 (s, 2H), 4.67 (d, J = 15, 1H), 4.56 (d, J = 15, 1H), 3.63 (bm, 1H), 3.50 (d, J = 5, 1H), 3.46 (d, J = 5, 1H), 3.08 (d, J = 15, 2H), 2.94 (d, J = 2.4, 1H), 2.89 (m, 1H), 1.64 (s, 4H).

MS: APCI (-): 449 (M-H);

LC-MS: s, 95 %

EXAMPLE 43



7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid, trifluoroacetic acid salt.

To a stirred solution of a mixture of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester and 2-amino-5-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.7 g, 16 mmol) was added diisopropylethylamine (2.8 ml, 16 mmol) and succinimidyl-2,2,2-trichloroethylcarbonate (4.8 g , 16 mmol) portion wise. The reaction mixture was stirred at room temperature for 18 h,

washed with saturated sodium hydrogen carbonate, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was chromatographyed on sillica (90 g) using a mixture of ethyl acetate/heptane (1:1) as eluent. Pure fraction were collected and the solvent evaporated in vacuo affording 6.78 g of crude product which was dissolved in dichloromethane (5 ml) followed by heptane (30 ml) which was added as a top layer. After crystallisation and filtration 5.44 g (74 %) of 2-amino-7-((2,2,2-trichloro-ethoxycarbonyl-amino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester was obtained as an oil.

^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.78 (m, 2H), 3.32 (m, 1H), 3.62 (m,1H), 3.72 (m,1H), 4.15 (m, 1H), 4,68 (m, 1H), 4.71 (s, 2H), 6.00 (s, 2H).

The above 2-amino-7-((2,2,2-trichloro-ethoxycarbonylamino)methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (4.0 g, 8.0 mmol) was dissolved in a mixture of tetrahydrofuran (15 ml) and a aqueous phosphate buffer (pH 3; 5 ml) followed by addition of zinc (16 g, 0.244 mol). The reaction mixture was stirred for 6 h at room temperature at which time the solvent was removed in vacuo. To the residue was added diethyl ether (20 ml) and water (40 ml). Sodium carbonate was added to the aqueous phase until pH = 8 and the aqueous phase was extracted with dichloromethane (3x). The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography on sillicagel (90 g) using a mixture of dichloromethane/ethanol/25 % ammonia in water 100:10:0.7 as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 1.52 g (61 %) of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.69 (dt, 2H).

Calculated for $C_{13}H_{20}N_3O_3S$;
C, 54.91 %; H, 7.09 %; N, 9.85 %. Found:
C, 54.53 %; H, 7.19 %; N, 9.61 %.

LC-MS : Mw = 285,2 R_t= 4.14 min

To a solution of Boc-D-phe-OH (0.28 g, 1.05 mmol) in dichloromethane (10 ml) was added 1-hydroxy benzotriazole (0.14 g, 1.05 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimid hydrochloride (0.18 g, 1.054 mmol). The reaction mixture was stirred for 15 min at room temperature. 2-Amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.30 g, 1.054 mmol) dissolved in dichloromethane (15 ml) was added. Ethyl diisopropylamine (0.18 ml, 1.05 mmol) was added and the reaction mixture was stirred over night at room temperature. The reaction was washed with 10 % aqueous citric acid (15 ml), saturated aqueous sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent removed in vacuo affording 594 mg (100 %) of 2-amino-7-(((1R)-2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester.
^{1}H NMR($CDCl_3$) δ 1.42 (s, 9H), 1.55 (s, 9H), 2.73 (m, 2H), 3.05 (m, 2H), 3.16 (m, 1H), 4.06 (m, 1H), 4.32 (m,1H), 5.05 (s, 1H), 6.01 (s, 2H), 6.10 (s, 1H), 7.20 (m, 5H).

LC-MS : Mw = 532.2, R_t = 7.11.

2-Amino-7-(((1R)-2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)-methyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.58 g, 1.09 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.3 ml, 2.18 mmol) was added and the reaction mixture was cooled with in a ice bath. Imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.43 g, 2.18 mmol) dissolved in dichloromethane (5 ml) was added to the

reaction mixture. The reaction mixture was stirred overnight at room temperature diluted with dichloromethane (20 ml), washed with 1 N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate (15 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography sillicagel (40 g) using a mixture of ethyl acetate/heptane 1:1 as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 512 mg (69 %) of 7-((1R)-(2-*tert*-butoxycarbonylamino-3-phenyl-propionylamino)methyl)-2-(*tert*-butoxyoxalylamino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

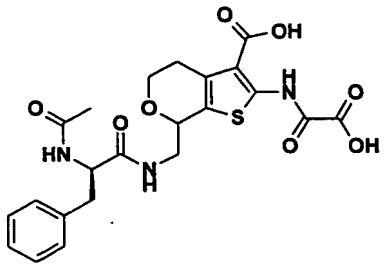
^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.59 (s, 9H), 1.61 (s, 9H), 2.86 (m, 2H), 3.02 (m, 2H), 3.15 (m, 1H), 3.64 (m, 1H), 3.87 (m, 1H), 4.09 (m, 1H), 4.28 (m, 1H), 4.51 (m, 1H), 4.67 (m,1H), 5.10 (s, 1H), 6.00 (s, 1H), 7.20 (m, 5H), 12.5 (s, 1H).

7-((1R)-(2-*tert*-Butoxycarbonylamino-3-phenyl-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyrran-3-carboxylic acid *tert*-butyl ester (0.51 g, 0.76 mmol) was dissolved in dichloromethane (5 ml). Trifluoroacetic acid (5 ml) was added and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo (stripped 3 times with dichloromethane) which afforded 314 mg (92 %) of the title compound.

Calculated for $C_{20}H_{21}N_3O_7S$; 1 x CF_3COOH, 1 x H_2O;
C, 45.60 %; H, 4.17 %; N, 7.25 %. Found:
C, 45.78 %; H, 4.20 %; N, 7.05 %.

LC-MS : RT=3.61 / RT=3.77 Mw = 448.2

EXAMPLE 44



7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

To a mixture of Ac-D-Tyr-OH (235 mg, 1.05 mmol) dissolved in dichloromethane (10 ml) was added 1-hydroxybenzotriazole (0.14 g, 1.05 mmol), 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride (0.20g , 1.05 mmol) and the reaction mixture was stirred for 15 min at room temperature. 2-Amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 1.05 mmol) dissolved in dichloromethane (10 ml) was added followed by N,N-diisopropyl-ethylamine (0.18 ml, 1.05 mmol). The resulting reaction mixture was stirred for 18 h at room temperature, diluted with dichloromethane (15 ml) was washed with 10 % aqueous citric acid (25 ml), saturated sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography on sillicagel (40 g) using ethyl acetate as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 304 mg (59 %) of 7-((2-acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil. ^{1}H NMR ($CDCl_3$) double set of peaks from diastereomers; selected peaks: δ 1.55 (s, 9H), 1.95 (s, 3H), 2.74 (m, 2H), 2.92 (m, 2H), 3.23 (m, 1H), 3.63 (m, 2H), 6.05 (s, 2H).

LC-MS: R_t = 5.17, Mw = 490.4

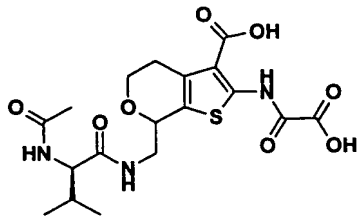
7-((2-Acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.3 g, 0.61 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.17 ml, 1.22 mmol) was added and the reaction mixture was cooled to 0° C. Imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.24, 1.22 mmol) dissolved in dichloromethane (10 ml) was added dropwise. The resulting reaction mixture was stirred at room temperature for 18 h. Dichloromethane (20 ml) was added and the mixture was washed with 1 N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate (20 ml), dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by flash chromatography on sillicagel (40 g) using ethyl acetate as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 208 mg (55 %) of 7-((2-acetylamino-3-(4-hydroxy-phenyl)-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.
LC-MS : Mw = 618.4, R_t = 6.97

7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.2 g, 0.32 mmol) was dissolved in dichloromethane (8 ml) and trifluoroacetic acid (4 ml) was added. The reaction mixture was stirred 7 h at room temperature. The solvent was evaporated in vacuo (stripped 3 times with dichloromethane) which afforded 200 mg (100 %) of the title compound.

Calculated for $C_{22}H_{23}N_3O_9S$, 3 x H_2O;
C, 47.22 %; H, 5.22 %; N, 7.51 %. Found:
C, 47.05 %; H, 4.88 %; N, 7.39 %.

LC-MS : R_t = 3.64, Mw = 506.4.

EXAMPLE 45



7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid.

To a solution of Ac-D-Val-OH (0.17 g, 1.09 mmol) dissolved in dichloromethane (15 ml) was added N,N-dimethylformamide (1 ml), 1-hydroxybenzotriazole (0.15 g, 1.09 mmol) and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (0.21 g, 1.09 mmol). The reaction mixture was stirred for 15 min. at room temperature at which time a solution of 2-amino-7-aminomethyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.31 g, 1.09 mmol) in dichloromethane (10 ml) was added followed by N-N-diisopropylethylamine (0.186 ml, 1.09 mmol). The resulting mixture was stirred over night at room temperature diluted with dichloromethane (10 ml) washed with 10 % aqueous citric acid (20 ml), sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo affording 415 mg (90 %) of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.
^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H), 0.98 (t, 2H), 1.55 (s, 9H), 2.02 (d, 1H), 2.77 m, (2H), 3.40 (m, 1H), 4.14 (m, 1H).
LC-MS : R_t = 5.17 Mw = 426.4

To a mixture of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-amino-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.4 g, 0.94 mmol) dissolved in dichloromethane (10 ml) and triethylamine (0.26 g, 1.87 mmol) cooled to 0 °C was added a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.37 g, 1.87 mmol) in dichloromethane (10 ml).

The resulting mixture was stirred for 18 h at room temperature diluted with dichloromethane (20 ml) washed with 1N hydrochloric acid (15 ml), saturated sodium hydrogencarbonate, dried ($MgSO_4$), filtered and the solvent evaporated in vacuo which afforded 515 mg (97 %) of 7-((2-acetylamino-3-methyl-butyrylamino)methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester as an oil.

LC-MS: R_t = 7.11, Mw = 554.4.

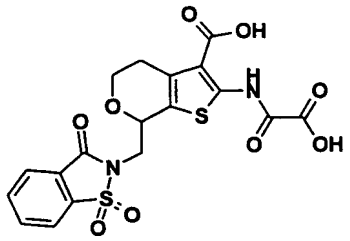
HPLC: R_t = 34.16, Area (%) = 100 %.

To a solution of the above 7-((2-acetylamino-3-methyl-butyrylamino)-methyl)-2-(*tert*-butoxyoxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid *tert*-butyl ester (0.5 g, 0.90 mmol) dissolved in dichloromethane (3 ml) was added trifluoroacetic acid (1 ml) and the reaction mixture was stirred for 18 h at room temperature. Trifluoroacetic acid (4 ml) was added and the mixture was stirred for an additional 3 h at room temperature. The volatiles were evaporated in vacuo (and stripped 3 times with dichloromethane) affording 282 mg (71 %) of the title compound.

Calculated for $C_{18}H_{23}N_3O_8S$, 2 x H_2O;
C, 45.28 %; H, 5.70 %; N, 8.80 %. Found:
C, 45.20 %; H, 5.50 %; N, 8.80 %.

LC-MS: R_t = 3.60, Mw = 442.2

EXAMPLE 46



2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

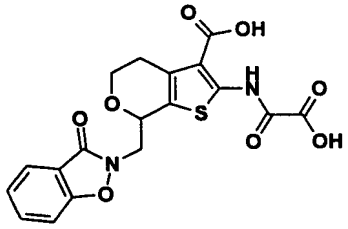
M.p.: 210 - 212 °C;

Calculated for $C_{18}H_{14}N_2O_9S_2$, 0.5 x H_2O, 0.75 x Ethyl acetate;

C, 44.49 %; H, 3.83 %; N, 5.32 %. Found:

C, 44.70 %; H, 3.61 %; N, 4.90 %.

EXAMPLE 47



2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid

The title compound was prepared in a similar way as described in Example 25.

M.p.: 236 - 237 °C;

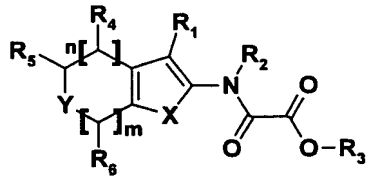
Calculated for $C_{18}H_{14}N_2O_8S$, 0.3 x H_2O;

C, 51.02 %; H, 3.47 %; N, 6.61 %. Found:

C, 51.16 %; H, 3.47 %; N, 6.31 %.

CLAIMS

1. A compound of Formula 1



Formula 1

wherein

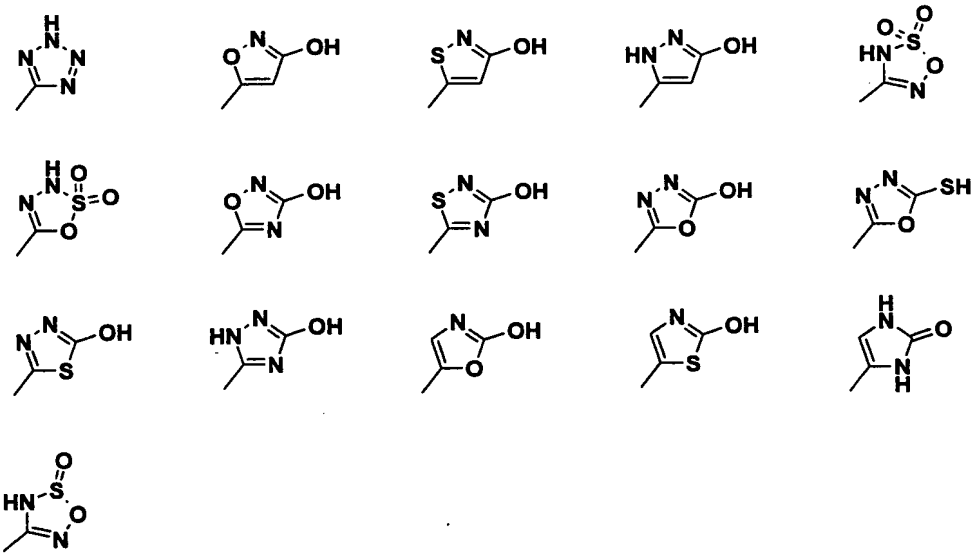
n is 0, 1 or 2;

m is 1 or 2;

X is S or O;

Y is O, S, SO or SO_2;

R_1 is hydrogen or $COOR_3$, or R_1 is selected from the group consisting of the following 5-membered heterocycles:



R_2 is hydrogen, C_1-C_6alkyl, hydroxy or NR_7R_8;

R_3 is hydrogen, C_1-C_6alkyl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyloxyC_1-C_6alkyl or C_1-C_6alkylcarbonyloxyarylC_1-C_6alkyl;

R_4, R_5 and R_6 are independently hydrogen, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6-alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkyl-thio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylaminoC_1-C_6alkyl, aryl-C_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkyl-carbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6-alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkyl-carboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_8C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonyl-amino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing from 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulphur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6-alkyloxyC_1-C_6alkyl, C_1-C_6alkylamino-C_1-C_6alkyl or NR_9R_{10}, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-

C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6-alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form.

2. A compound according to claim 1 wherein X is sulphur.

3. A compound according to claim 2 wherein R_1 is $COOR_3$ and R_2 is hydrogen; wherein R_3 is defined as above.

4. A compound according to claim 3 wherein n and m are 1.

5. A compound according to claim 4 wherein Y is oxygen.

6. A compound according to claim 3 wherein R_5 is C_1-C_6alkylNR_7R_8.

7. A compound according to claim 6 wherein R_4 and R_6 are hydrogen.

8. A compound according to claim 2 wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, R_5 is C_1-C_6alkylNR_7R_8 and Y is oxygen.

9. A compound according to claim 2 wherein R_1 is 5-tetrazolyl, R_2 is hydrogen, R_6 is C_1-C_6alkylNR_7R_8 and Y is oxygen.

10. A compound according to claim 5 wherein R_6 is C_1-C_6alkylNR_7R_8.

11. A compound according to claim 10 wherein R_4 and R_5 are hydrogen.

12. A compound according to claim 10 and 11 wherein R_7 and R_8 are together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system.

13. A compound according to claim 12 wherein the ring system is 1,3-dihydro-benzo[d]isothiazolyl, substituted with 2 or 3 oxo groups at the atom positions adjacent to the nitrogen atom.

14. 2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

15. A compound selected from the following:
5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester methyl ester;
Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester;
7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester;

7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-[4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(1,3-Dioxo-1,3-dihydro-isoindol-2-yloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[3-(2,4-Dimethoxy-phenyl)-ureidomethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)-carbamoyl)-nicotinic acid;

5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Benzyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-[(2-Amino-3-phenyl-propionylamino)-methyl]-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(5-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

16. Compounds according to any one of the preceding claims which acts as inhibitors of Protein Tyrosine Phosphatases.

17. A pharmaceutical composition comprising a compound according to any of the claims 1 to 15 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

18. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 15 or a

pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

19. A pharmaceutical composition suitable for treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising a compound according to any of the claims 1 to 15 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

20. The pharmaceutical composition according to claim 17, 18 or 19 in the form of an oral dosage unit or parenteral dosage unit.

21. A pharmaceutical composition according to claim 17, 18 or 19 wherein said compound is administered as a dose in a range from about 0.05 to 1000 mg, preferably from about 0.1 to 500 mg and especially in the range from 50 to 200 mg per day.

22. A compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for

therapeutical use.

23. A compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

24. A compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

25. The use of a compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

26. The use of a compound according to any of the claims 1 to 15 for preparing a medicament.

27. The use of a compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament suitable for the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

28. The use of a compound according to any one of the claims 1 to 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament suitable for the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

29. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 15 to said subject.

30. A method of treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone,

diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 15 to said subject.

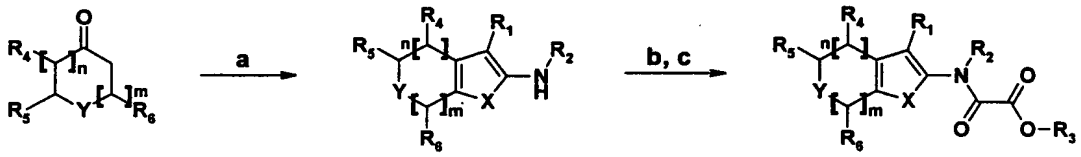
31. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity which process comprising bringing a compound according to any of the claims 1 to 15 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

32. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases which process comprising bringing a compound according to any of the claims 1 to 15 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

33. Any novel feature or combination of features as described herein.

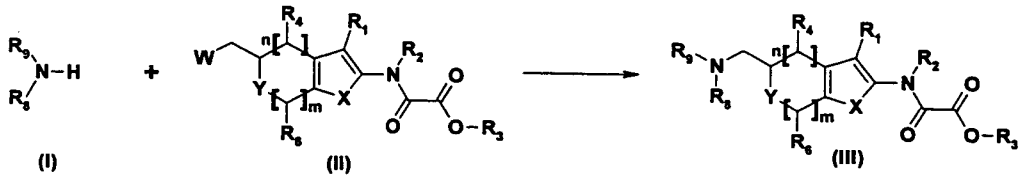
34. A method for preparing a compound of formula 1, characterized in

A)



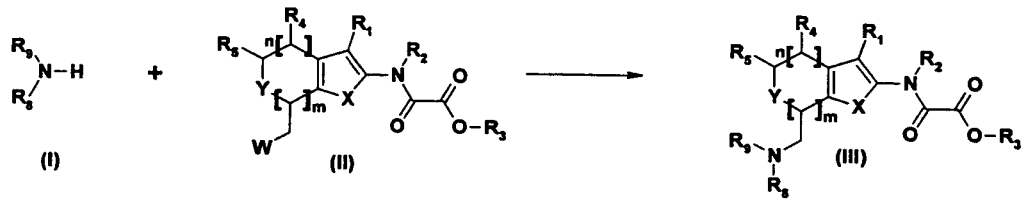
a) $NCCH_2COOR_3$, sulphur, morpholine or triethylamine, EtOH; b) R_3OCOCOimidazole, THF; c) 25 % TFA/CH_2Cl_2; wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5, and R_6 are defined above;

B)



By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, *Synthesis*, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, Y, R_1, R_2, R_3, R_4, R_6, R_8 and R_9 are defined above.

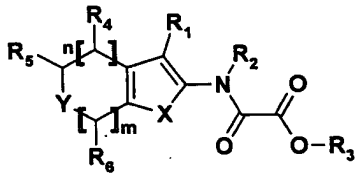
C)



By allowing an amine (I) and a substituted oxalylamide (II) to react under basic conditions (e.g. K_2CO_3, in N,N-dimethylformamide or methylethylketone) or under Mitsunobu conditions (Oyo Mitsunobu, *Synthesis*, (1981) 1-28) to yield (III) wherein W is OH, OSO_2Me or halo, and n, m, X, Y, R_1, R_2, R_3, R_4, R_5, R_8 and R_9 are defined above.

ABSTRACT OF THE INVENTION

The present invention provides novel compounds, novel compositions, methods of their use, and methods of their manufacture, where such compounds of Formula 1 are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPases) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like,



Formula 1

wherein n, m, X, Y, R_1, R_2, R_3, R_4, R_5 and R_6 are defined more fully in the description.

The compounds are useful in the treatment of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, and other diseases.